REVIEW

Potential role of ubiquinone (coenzyme Q10) in pediatric cardiomyopathy

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Summary Pediatric cardiomyopathy (PCM) represents a group of rare and heterogeneous disorders that often results in death. While there is a large body of literature on adult cardiomyopathy, all of the information is not necessarily relevant to children with PCM. About 40% of children who present with symptomatic cardiomyopathy are reported to receive a heart transplant or die within the first two years of life. In spite of some of the advances in the management of PCM, the data shows that the time to transplantation or death has not improved during the past 35 years.

Coenzyme Q10 is a vitamin-like nutrient that has a fundamental role in mitochondrial function, especially as it relates to the production of energy (ATP) and also as an antioxidant. Based upon the biochemical rationale and a large body of data on patients with adult cardiomyopathy, heart failure, and mitochondrial diseases with heart involvement, a role for coenzyme Q10 therapy in PCM patients is indicated, and preliminary results are promising. Additional studies on the potential usefulness of coenzyme Q10 supplementation as an adjunct to conventional therapy in PCM, particularly in children with dilated cardiomyopathy, are therefore warranted.

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Introduction

Pediatric cardiomyopathy (PCM) encompasses a group of uncommon and heterogeneous disorders often resulting in death. While there is a large body of literature on adult cardiomyopathy, not all of the information applies to children with PCM. It has been reported that about 40% of children with symptomatic cardiomyopathy will require a heart transplant or die within the first two years of life,\(^1\) and despite advances in the management of the disease, there is no change in the time to transplantation or death during the past 35 years.\(^3,4\) In this review, the potential therapeutic value of coenzyme Q10 (also known as ubiquinone) as an adjunct to conventional therapy in the management of PCM is discussed with particular reference to dilated cardiomyopathy.

Epidemiology of PCM

PCM is a rare form of cardiac disease in infancy, and its prevalence has been reported to be 10 per 100,000 based on an epidemiologic study that included all categories of PCM.\(^5\) According to Lipshultz et al.,\(^6\) this is an overestimate since the study did not exclude secondary cardiomyopathy in children. According to the Children’s Cardiomyopathy Foundation (USA), PCM occurs in approximately 12 children out of every million, with about 1000–5000 new cases diagnosed each year. This figure is very close to the estimate of 1.13 cases per 100,000 recently reported for the incidence of PCM in two regions of the US.\(^6\) Although prevalence would be higher than the incidence in the adult population, given the very small numbers involved and the narrow range in the pediatric age group, there would not be much difference between the two estimates.\(^6\) Results of another recent study carried out in Australia are very similar and they show an incidence of 1.24 per 100,000 children.\(^7\) The fact that the findings on incidence/prevalence are similar in geographically distinct regions suggests that genetic factors may play an important role in the development of PCM.\(^6,8\) The incidence of PCM is significantly higher in the first year of life than at older ages, and furthermore, the rates appear to be higher in black and Hispanic children.\(^6\)

Possible causes of PCM

Because of the fact that PCM is a rare disease, there has been little research or interest in exploring new treatment strategies, and therefore, the causes remain not well understood. WHO classification of cardiomyopathy involves three main categories: dilated or congestive, hypertrophic, and restrictive. Majority of cases in PCM are known to involve dilated and hypertrophic cardiomyopathies.\(^9\) According to the Pediatric Cardiomyopathy Registry (USA), approximately 79% of PCM cases are still of unknown origin, which is a much higher percentage than in the adult population. Furthermore, the underlying causes of cardiomyopathy in infants and children may be considerably different from those diagnosed in adults with similar symptoms. PCM is more likely to be related to genetic factors while lifestyle or environmental factors play a greater role in adult cardiomyopathy. In rare cases, PCM appears to be a symptom of a larger genetic disorder that may not be immediately apparent. As an example, when an infant or young child is diagnosed with dilated cardiomyopathy, a rare genetic heart disease called Barth Syndrome or any one of the rare mitochondrial diseases called mitochondrial cytopathies such as Kearns-Sayre syndrome may be the underlying cause. Likewise, a child with severe hypertrophic cardiomyopathy may actually be suffering form Noonan Syndrome, Pompe disease (type II glycogen storage disease), a fatty acid oxidation disorder (that may involve carnitine), or mitochondrial hypertrophic cardiomyopathy. Apart from differences in the cause and symptoms exhibited, the progression of cardiomyopathy may also be different in children. When children are diagnosed at an early age, the prognosis is generally poor depending on the form of cardiomyopathy and also the stage. Dilated cardiomyopathy is known to progress quite rapidly in young children. A significant number of children with dilated cardiomyopathy (up to about 40%) are known to fail medical management within the first year of
diagnosis, and of those who survive may suffer permanent damage to the heart. Mortality and heart transplant rates of PCM patients are also much higher than those in adults. This is likely to be due to the more fragile state of infants and young children, or it may also be due to the advanced progression of the disease that may be associated with another genetic disorder. Another unfortunate reason is that PCM is not usually detected until the end stage when obvious symptoms of heart failure become apparent. Cardiomyopathy can be easily missed in routine check-ups when there are no obvious features such as heart murmur or when there is no particular reason for diagnostic testing. This would include lack of family history of heart disease or other underlying factors.

**Acquired PCM**

PCM is one of the leading causes of cardiac death in infants and children. A large number of cases are known to be familial conditions that are genetically transmitted, but the disease can also be acquired during childhood. The most common cause for acquired cardiomyopathy is viral myocarditis, an infection that can be damaging to the heart muscle. Other causes for acquired cardiomyopathy include cardiovascular conditions such as Kawasaki disease, congenital heart defect, hypertension, cardiac transplantation or surgery, infectious or inflammatory diseases, immunologic diseases such as HIV, and also chemotherapy-induced cardiomyopathy. Dietary deficiencies may also be involved in some cases.

**Prognosis of PCM**

Although there are numerous possible causes for cardiomyopathy in children, few of them are directly treatable and most of the treatments currently available are aimed at treating the symptoms. Unfortunately, at present there is no cure or satisfactory treatment for PCM that can bring the heart to a healthy state and function, or assure long-term survival. Although sometimes children with certain types of cardiomyopathy are known to improve, a large majority of them do not show any improvement or recovery of impaired heart function. If PCM is detected in the earlier stages, both dilated and hypertrophic cardiomyopathies in children may be controlled with long-term drug therapy and also with the placement of a pacemaker if necessary.9

Currently, the long-term outlook for PCM remains unpredictable and rather grim because of its occurrence with a wide spectrum of severity and also outcome. Even if a child has a family history of the disease, the degree can vary considerably from the parents or siblings. The overall prognosis for a child also depends on the type of cardiomyopathy and the stage when the disease is first diagnosed. Sometimes children without obvious signs and symptoms or a family history of heart disease are either not diagnosed at all or not diagnosed early enough so that sudden cardiac death or progressive heart failure could be prevented. Although there is no cure for cardiomyopathy at this time, some of the symptoms and complications can be managed and controlled with appropriate medication and also implantable devices. Some children may stabilize with proper treatment and they may be able to have fairly normal lives possibly with some restrictions on exercise capacity. Children with more complex or severe forms of cardiomyopathy may have additional limitations such as developmental delays or requiring specialized care. A heart transplant may be one option but this would be at the expense of other possible medical complications. The treatment outcome of PCM patients is in sharp contrast to the achievements in the treatment of congenital heart disease in children. The availability of state-of-the-art diagnostic tools has not yet altered the death rate or the need for transplantation in PCM, and transplantation is unlikely to result in normal life expectancy in children with PCM.10 The economic and social costs of PCM are also considerable. The cost of dealing with PCM was estimated to be about $200 million a year in the US according to earlier calculations made over two decades ago11,12 and it would certainly be much higher today. Thus, there is an urgent need for more innovative and effective treatments for PCM at this time.

**Rationale for a role of coenzyme Q10 in PCM**

Coenzyme Q10, also known as ubiquinone, is a naturally occurring substance that is synthesized in the body. It was originally isolated from beef heart mitochondria in 1957.13 Coenzyme Q10 is a lipid-soluble molecule with characteristics similar to those of vitamins. Relatively high concentrations of coenzyme Q10 are found in the mitochondria of cells where it has a critical role in energy production. Tissues with high-energy requirements such as the heart, kidney, liver, and skeletal muscle contain higher amounts of coenzyme Q10.14

The clinical evidence for a potential role of coenzyme Q10 in PCM is based primarily upon data from adult heart failure patients. Coenzyme Q10
has been successfully used as an adjunct to conventional therapy in treating adult patients with several types of heart disease for over three decades, and much of the data relates to those with cardiomyopathy and congestive heart failure.\textsuperscript{15,16} The biochemical rationale for the use of coenzyme Q10 is based upon its mechanism of action, primarily the fact that it plays a pivotal role in the bioenergetics of the heart muscle.\textsuperscript{14,17} It is an obligatory and a rate-limiting cofactor in mitochondrial adenosine triphosphate (ATP) production.\textsuperscript{17} Coenzyme Q10 is a crucial component of the electron transport chain (respiratory chain) in the mitochondria where energy is generated as ATP that drives all cellular machinery and biosynthetic processes.\textsuperscript{14,17–19} Coenzyme Q10 is essential for the activities of complexes I, II and III enzyme systems in the electron transport chain, and it shuttles electrons from complexes I (NADH-ubiquinone reductase) and II (succinate-ubiquinone reductase) to complex III (ubiquinol-cytochrome c reductase). Thus, coenzyme Q10 which refers to both the oxidized and reduced forms of the redox pair (as ubiquinone and ubiquinol, Fig. 1) plays a critical role in cellular energy production. This bioenergetic function of coenzyme Q10 is of fundamental importance in its clinical application, particularly as it relates to cells with exceedingly high metabolic demands such as the cardiac myocytes. While endogenous production is the primary source of coenzyme Q10 in the body, it does not meet the requirements under certain stressed or pathologic conditions. Because of its crucial role in mitochondrial energy production, numerous systems are affected when the availability of coenzyme Q10 becomes limiting, and tissues with high energy demands such as the heart are more readily affected. In fact, coenzyme Q10 deficiency has been observed in patients with heart disease.\textsuperscript{20} Impaired coenzyme Q10 status appears to have a direct bearing on the pathophysiology of cardiomyopathy, especially in the case of dilated cardiomyopathy, since this condition has been shown to involve defective bioenergetics or energy deficiency in the myocytes eventually leading to heart failure.\textsuperscript{15,16,20–22}

Coenzyme Q10 has other important functions. It is a potent antioxidant, a feature that has important implications in heart function, especially under conditions of reperfusion injury to the heart muscle. The role of free radicals and their destructive potential in causing cell injury and in cell death in settings of ischemia-reperfusion are now well recognized. The antioxidant properties of coenzyme Q10 in its reduced form as ubiquinol and its localization within the mitochondria, a major source of free radicals, further potentiate its therapeutic value in protecting and promoting proper functioning of the heart. It functions as the first line antioxidant defense during lipid peroxidation process, and furthermore, it has an important role in the regeneration of other antioxidants. For instance, coenzyme Q10 as ubiquinol can regenerate vitamin E (alpha tocopherol) from its phenoxyl radical form and the ubiquinone formed in this process is reduced back to ubiquinol in the electron transport chain.\textsuperscript{23} Protection of LDL from oxidation is yet another important antioxidant function of coenzyme Q10 that has an important bearing in maintaining overall cardiovascular health.\textsuperscript{14,15,24,25} Under certain laboratory conditions, coenzyme Q10 may show prooxidant properties by way of superoxide production in the respiratory chain,\textsuperscript{26} however such a prooxidant effect has not been observed in vivo when high doses are ingested by human subjects.\textsuperscript{24} Among the other important properties of coenzyme Q10 are membrane stabilization, inhibition of cell death, and signal transmission.\textsuperscript{17,18}

**Role of coenzyme Q10 in cardiomyopathy and heart failure in adults**

The primary biochemical basis for the use of coenzyme Q10 in the treatment of various types

![Ubiquinone (2,3-Dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone)](image1)

![Ubiquinol (2,3-Dimethoxy-5-methyl-6-decaprenyl-1,4-benzohydroquinone)](image2)

**Figure 1** Structure of coenzyme Q10. Ubiquinone (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) and ubiquinol (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzohydroquinone).
of cardiomyopathy in adults lies in the fact that coenzyme Q10 has a critical role in mitochondrial bioenergetics, and the underlying pathophysiology involves defective bioenergetics, specifically availability of ATP that plays a central role in regulating myocardial contractility. A significant correlation has been demonstrated in the diseased heart between ATP content and systolic and diastolic left ventricular indices. Myocardial deficiency of coenzyme Q10 has also been documented in patients with cardiomyopathy that can explain the underlying energy deficit in the heart muscle that could lead to impaired function. There is clear-cut evidence to show that coenzyme Q10 acts at the mitochondrial level to improve the efficiency of energy production in human heart tissue. This is demonstrated by its localization and relative abundance in the mitochondria and its fundamental role in mitochondrial bioenergetics. The antioxidant properties of coenzyme Q10 also have an important role in protecting the mitochondria from free radical damage and thus maintain its integrity and function. Another interesting mechanism that has been suggested is that coenzyme Q10 aids heart function in heart failure patients by way of its inotropic action. Such action increases the contractile force of the heart to improve cardiac output.

Pioneering studies on the efficacy of coenzyme Q10 supplementation in adult patients with heart failure were first carried out in Japan in the 1960s and 1970s. Since these early investigations, there has been a slow but steady accumulation of clinical experience in several countries for over three decades with the use of coenzyme Q10 as an adjunct to conventional therapy in adults with various types of cardiomyopathy, congestive heart failure and other forms of heart disease. This is accompanied by a large body of supportive data from laboratory and preclinical studies and collectively, the data gathered over the years document the efficacy and also the safety of coenzyme Q10 in patients with heart failure and other heart ailments. There have been over 15 randomized controlled clinical trials with both primary and secondary forms of heart failure, in addition to numerous open-label trials. In a meta-analyses of controlled clinical trials conducted during the years 1986–1995, eight of the 14 trials met the inclusion criteria for reliable meta-analyses, and seven out the eight studies documented significant improvement in various parameters of heart function in adult patients with cardiomyopathy and congestive heart failure of varying etiologies (idiopathic, dilated, ischemia, hypertension, valvular heart disease, and congenital heart disease). Significant functional improvement was evident specifically with respect to stroke volume, cardiac output, cardiac index, and end-diastolic volume in patients treated with coenzyme Q10.

The largest controlled trial to date on adult cardiomyopathy and congestive heart failure was reported in 1993 that involved a total of 641 patients. This was a double-blind placebo-controlled study with NYHA class III and IV patients using a dose of 2 mg CoQ10 per kg per day or placebo for one year. The results showed significant improvements in arrhythmias and episodes of pulmonary edema, and reduction in the number of hospital admissions and in the overall mortality rate in the treated group. The improvement in the overall quality of life of patients along with the reduction in hospitalizations in the coenzyme Q10 group also indicates highly significant savings in health care costs. This study was followed by a small double-blind cross-over trial by the same investigators where a noninvasive radionuclide scanning was employed to examine changes in ejection fraction, stroke volume and cardiac output in chronic heart failure patients. Significant improvements were again documented in all these measures in patients treated with 150 mg of coenzyme Q10 per day for just four weeks. Following this study, another controlled cross-over study was conducted involving 79 patients with severe chronic cardiomyopathy and congestive heart failure who were treated with coenzyme Q10 at 100 mg per day for three months. Significant improvements in volume load ejection fraction, arteriovenous oxygen difference and quality of life assessment were documented. In a more recent controlled trial with 22 heart failure patients (NYHA class II and III) treated with 200 mg of coenzyme Q10 per day for three months, a marked improvement in left ventricular ejection fraction was demonstrated. It should be emphasized here that in all these clinical trials, coenzyme Q10 was used as an adjunct to conventional therapy in adult patients.

In contrast to the numerous studies on heart failure discussed above that have yielded positive results, an improvement with coenzyme Q10 was not observed in three controlled trials. The results were neutral in that no additional benefit with coenzyme Q10 supplementation over and above that obtained with conventional therapy could be demonstrated. The possible reasons for the lack of benefit with coenzyme Q10 have been addressed. Features common to these three studies that may have contributed to the neutral results are: sample size, severity and duration of the
disease, dosage of coenzyme Q10, and duration of treatment.15,16,49,50 Another issue here is the importance of plasma coenzyme Q10 measurements. It is important to ascertain that the plasma concentrations are indeed in the therapeutic range, but this is often overlooked. Following a recent review of 34 controlled trials including the neutral study by Permanetter et al.46 and several open-label and long-term studies, Langsjoen and Langsjoen16 concluded that there was strong evidence to show that coenzyme Q10 alters the history and has the potential to reduce the risk and prevent cardiovascular disease by the maintenance of optimal cellular and mitochondrial function in cardiomyocytes. The benefits of coenzyme Q10 supplementation go beyond the correction of a possible deficiency since risk reduction and clinical improvements are frequently seen in subjects with possible deficiency since risk reduction and clinical supplementation go beyond the correction of a cardiomyocytes. The benefits of coenzyme Q10 supplementation go beyond the correction of a possible deficiency since risk reduction and clinical improvements are frequently seen in subjects with possible deficiency since risk reduction and clinical supplementation go beyond the correction of a variety of neuromuscular problems. Because the myocardium depends heavily on mitochondrial energy production, it is not surprising that genetic errors of mitochondrial function often result in cardiomyopathy. The etiology of these types of mitochondrial cardiomyopathy involves mutations in both the nuclear DNA and mitochondrial DNA, leading to impaired bioenergetics. Although these mutations often cause multisystem disorders, cardiac involvement happens to be a major component.51,52 Numerous studies over the past two decades have clearly documented the potential clinical benefit with the use of coenzyme Q10 in treating cardiomyopathy and also the associated neuromuscular disorders in children and adults with mitochondrial diseases.53–56 The beneficial effect observed with the use of coenzyme Q10 is consistent with the view that increased cofactor concentration in the mitochondria increases the efficiency of oxidative phosphorylation and enhances energy (ATP) production.16,51,54 In this context, it is interesting note a case report where idebenone, a synthetic analog of coenzyme Q10, was also found to be beneficial in a mitochondrial cardiomyopathy patient showing depletion of coenzyme Q10 in the myocardial tissue.57 However, its unapproved drug in the US whereas coenzyme Q10 is a nutrient that is readily available as a dietary supplement.

In an important publication appearing as case report recently, Elshershari et al. have demonstrated the potential usefulness of coenzyme Q10 in treating PCM. This appears to be the first such study on the use of coenzyme Q10 in PCM. In this trial, children two months to 11 years old with idiopathic dilated cardiomyopathy, were stabilized first and then treated with oral coenzyme Q10 at a dose of 10 mg per kg per day as an adjunct to conventional therapy. Overall, there was a highly significant improvement in their cardiac function. Five of the six children improved by two NYHA classes and one by one NYHA class. The objective measures were improvement in fractional shortening (17.3–30%) and increase in ejection fraction (41–60%). Although the sample size in this study was small, the findings are indeed very promising and need to be followed up.

**Use of coenzyme Q10 in PCM**

In addition to the documented beneficial effect of coenzyme Q10 in adults with cardiomyopathy, particularly dilated cardiomyopathy, and congestive heart failure, the potential therapeutic efficacy of coenzyme Q10 in PCM can be gleaned from studies on patients (both children and adults) with mitochondrial cytopathies, another group of rare diseases. Cardiomyopathy is frequently observed in such patients who have a diagnosis of electron transport chain or respiratory chain disorder. These disorders represent a rather wide spectrum of inherited diseases due to mitochondrial dysfunction that are often associated with serious impairment in heart function including cardiomyopathy along with a variety of neuromuscular problems. Because the myocardium depends heavily on mitochondrial energy production, it is not surprising that genetic errors of mitochondrial function often result in cardiomyopathy. The etiology of these types of mitochondrial cardiomyopathy involves mutations in both the nuclear DNA and mitochondrial DNA, leading to impaired bioenergetics. Although these mutations often cause multisystem disorders, cardiac involvement happens to be a major component.51,52 Numerous studies over the past two decades have clearly documented the potential clinical benefit with the use of coenzyme Q10 in treating cardiomyopathy and also the associated neuromuscular disorders in children and adults with mitochondrial diseases.53–56 The beneficial effect observed with the use of coenzyme Q10 is consistent with the view that increased cofactor concentration in the mitochondria increases the efficiency of oxidative phosphorylation and enhances energy (ATP) production.16,51,54 In this context, it is interesting note a case report where idebenone, a synthetic analog of coenzyme Q10, was also found to be beneficial in a mitochondrial cardiomyopathy patient showing depletion of coenzyme Q10 in the myocardial tissue.57 However, its unapproved drug in the US whereas coenzyme Q10 is a nutrient that is readily available as a dietary supplement.

**Dosage of coenzyme Q10 and plasma values**

The dosage of coenzyme Q10 employed in treating mitochondrial disease patients (both children and adults) ranges from about 4 to 15 mg per kg per day according to the guidelines developed by Gold and Cohen.53 The same dosage range appears to be reasonable in treating patients with PCM. Plasma or serum measurements of coenzyme Q10 are very useful in any study involving coenzyme Q10 to assess its status and also to monitor response to coenzyme Q10 supplementation.59 Elegant HPLC methodologies are available for plasma coenzyme Q10 analysis,60 although currently only a few laboratories that are primarily involved in mitochondrial disease research are capable of running the assays properly. The mean plasma coenzyme Q10 concentration (total) in healthy children has been reported to be in the range (with SD) 0.84 ± 5.1.51 It should be noted here that plasma or serum coenzyme Q10 status does not necessarily
reflect tissue status and this may explain why clinical improvement is frequently observed in patients with apparently normal plasma values.

In conclusion, based upon the biochemical rationale and a large body of evidence on the clinical benefit in adults with various types of cardiomyopathy and heart failure, and also in children and adults with mitochondrial cytopathies, the outlook for coenzyme Q10 therapy in PCM is promising. Preliminary results on the use of coenzyme Q10 in children with dilated cardiomyopathy are encouraging. Controlled trials to explore the potential usefulness of coenzyme Q10 supplementation as an adjunct to conventional therapy in PCM, particularly in children with dilated cardiomyopathy, are therefore warranted.

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