*Original Article*

# Stimulatory effects of collagen production induced by coenzyme $Q_{10}$ in cultured skin fibroblasts

**Yukitoshi Mine,* Takayuki Takahashi, and Tadashi Okamoto**

Division of Health Sciences and Social Pharmacy, Faculty of Pharmaceutical Sciences, Kobe Gakuin University

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**Coenzyme $Q_{10}$ ($CoQ_{10}$) is a well-known antioxidant and serves as an essential carrier for electron transport and proton translocation in the mitochondrial respiratory chain. $CoQ_{10}$ has been widely commercially available in Japan as a dietary and health supplement since 2001 and it is used for the prevention of lifestyle-related diseases induced by aging. Recently, it was stated that for Japan, which is facing an aging society, $CoQ_{10}$ has been used in many skincare products. However, the physiological actions of $CoQ_{10}$ in skin fibroblasts are not fully understood. In this study, we examined the effect of $CoQ_{10}$ on cultured human skin fibroblast. In this study, $CoQ_{10}$ treatment increased intracellular $CoQ_{10}$ level and promoted proliferation of fibroblasts. In addition, $CoQ_{10}$ increased mRNA expression of type I, IV, VII collagen, elastin, and HSP47, whereas $CoQ_{10}$ has little effect on mRNA of type II and VIII MMP. These results suggested that $CoQ_{10}$ has the efficacy that it increases collagen production in skin, thereby there is possible of the anti-aging by $CoQ_{10}$ in Japan which reached an aging society, so that it might be based on new physiological function by $CoQ_{10}$.**

***Key Words***: **coenzyme $Q_{10}$, collagen, anti-aging, fibroblasts, elastin**

The skin is the body's largest organ with an area of approximately 2 $m^2$, and it consist of epidermis, dermis and subcutaneous tissue. The epidermis is outermost layers in the skin, and it is composed of stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum. The dermis is layers of skin between epidermis and subcutaneous tissue, and it consist of connective tissue. The fibroblasts have synthesized extracellular matrix (ECM) such as collagen, elastin, gelatin and fibronectin, which play skin physiological function. Collagen and elastin are the major fibrous proteins as connective tissue in skin. Collagen molecules have three α-chain that form a triple helix, which is one of ECM, has variety types and roles. For example, type I collagen form cross-striated fibrils with an axial periodicity of approximately 67 nm.[1] In addition, a part of basement membrane consists of type IV collagen. Moreover, type VII collagen connect basement membrane to dermis. Collagen fibrils do not stretch, whereas elastin is flexible and elastic fiber, which is structural protein capable of stretching in two dimensions. The basic subunit of elastin fibrils is tropoelastin, it has a molecular weight of about 72,000 and contains about 800 amino acid residues. Like collagen, it is rich in glycine and alanine. Furthermore, Matrix metalloproteinase (MMP) has been known as chemokine and catabolic enzyme of ECM, and it have been included in the group of inflammation enzyme. In particular, MMP play an important role in degradation of collagen. Collagen expression decreased in aged, whereas aging increased level of MMP caused more collagen degradation in skin.[2,3]

It is well known that coenzyme $Q_{10}$ ($CoQ_{10}$) serves as an essential carrier for electron transport and proton translocation in the mitochondrial respiratory chain, and it is composed of series of enzyme complexes embedded in the lipid bilayer of the inner mitochondrial membrane.[4,5] Besides its role in electron-transfer reactions, $CoQ_{10}$ is an effective lipid soluble antioxidant[6,7] that contribute to exclude a free radical, thereby preventing oxidative damage in the human body. $CoQ_{10}$ in the bodies of human beings is thought to be provided by both dietary intake, such as dietary foods and health supplements, and *de novo* biosynthesis.[8] From these research results, The Ministry of Health, Labour and Welfare in Japan permitted the use of $CoQ_{10}$ as a food additive as long as no claims were made about its pharmacological effectiveness and application, and $CoQ_{10}$ has been widely commercially available in Japan as a dietary and health supplement since 2001 and is used for the prevention of lifestyle-related diseases induced by aging. Recently, it was stated that for Japan, which is facing an aging society, $CoQ_{10}$ has been used in many skincare products and purpose of anti-aging substances. Then, while sales of dietary and health supplement products have been rapidly increasing in Japan, it is essential to supply quality-controlled products for consumers. As one of the causes of this thing, there is Hoppe *et al.*[9] paper that $CoQ_{10}$ is also reported to have anti-aging actions, it also *in vivo* where authors have demonstrated a reduction in skin wrinkles. After it is reported, several reports of $CoQ_{10}$ for the skin have been reported by different investigators.[10–12] However, investigators have used $CoQ_{10}$ of lipid soluble for all those reports. Recently, a part of $CoQ_{10}$ containing products with skincare and health supplement have distributed in Japan is included water soluble $CoQ_{10}$ containing products. Nevertheless, few studies have examined that effect of water soluble $CoQ_{10}$ in skin. In consequence, the physiological actions of water soluble $CoQ_{10}$ in human skin are not fully understood. Therefore, this paper describes that we investigated the effect of water soluble $CoQ_{10}$ in cultured human neonatal dermal fibroblasts.

## Materials and Methods

**Materials and cell culture.** $CoQ_{10}$ powder, PureSorb-QTM™40 (P40), which is containing 40 w/v% $CoQ_{10}$, was kindly donated by Nisshin Pharma Inc. (Tokyo, Japan) for this study.[13] High performance liquid chromatography (HPLC) solvents and ethanol were purchased (HPLC grade) from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemi-

*To whom correspondence should be addressed.
E-mail: softtennis045@gmail.com

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cals used were of analytical grade, available from commercial suppliers. Antibodies against type I collagen was obtained from COSMO BIO Co., Ltd. (Tokyo, Japan). Normal human dermal fibroblast (NHDF) was purchased from Lonza Co. Ltd. (Tokyo, Japan). Fibroblasts were grown in Dulbecco's modified Eagle's medium (DMEM; Nacalai Tesque, Kyoto, Japan) supplemented with 2% fetal bovine serum (FBS; MP Biomedicals, Illkirch, France), 2 mM glutamine, 100 units/ml penicillin and 100 mg/ml streptomycin (Nacalai Tesque). The cells were incubated under 37°C in a humidified atmosphere of 5% $CO_2$ and 95% air in a $CO_2$ incubator. After 24 h, culture medium was replaced by the DMEM containing 2% FBS and P40, and the cells were subsequently pre-cultured for 1 week in the $CO_2$ incubator for all experiments in this study.

**Measurement of $CoQ_{10}$ levels in human skin fibroblast.** $CoQ_{10}$ levels were measured by HPLC-electrochemical detector (HPLC-ECD) with the method of Okamoto *et al.*[14] Intracellualr $CoQ_{10}$ levels were expressed as μmol per mg protein.

**Protein assay.** Protein assay was performed to normalize with the Bradford method.[15]

**Cell proliferation assay.** Fibroblasts were seeded on 24-well plates ($1.0 \times 10^4$ cells per well) and cultured in DMEM containing 2% FBS for 24 h. Culture medium was then changed to DMEM which did not contain FBS for 3 days. After, cell proliferation was determined by cell counting kit-8 (Dojindo Laboratories, Kumamoto, Japan).[16] The results were expressed as percentage of untreated control.

**Real-time PCR.** Total RNA from cultured skin fibroblasts was prepared using a commercial kit (RNeasy Mini Kit; Qiagen, Chatsworth, CA) according to the manufacture's protocol. The mRNA expression was quantified by methods of TaqMan with Real-time reverse transcriptase PCR (RT-PCR). PCR primers were purchased from SIGMA-ALDRICH custom oligonucleotide synthesis service. Standard RT-PCR primers for human COL1: Forward, 5'-GGGATTCCCTGGACCTAAAG-3' and reverse, 5'-GGAACACCTCGCTCTCCA-3' and COL4: forward, 5'-AGGAGAGAAGGGCGCTGT-3' and reverse, 5'-TCCAGGTAA GCCGTCAACA-3' and COL7: Forward: 5'-GCTGGTGCT GCCTTTCTCT-3' and reverse: 5'-TCCAGGCCGAACTCT GTC-3' and MMP2: forward, 5'-CCCCAAAACGGACAA AGAG-3' and reverse, 5'-TGTCCTTCAGCACAAACAGG-3' and MMP8: forward, 5'-TGACAGAGACCTCATTTTCCTATT TA-3' and reverse, 5'-CTGCGTCAATTGCTTGGA-3' and HSP47: forward, 5'-TCCCTCTGAGGCAGTTTCC-3' and reverse, 5'-GCTGCAGGTTTCTTCACCTC-3'.

The PCR was semi-quantitative and the cycling conditions were 95°C for 10 min, 40 cycles of amplification at 95°C for 15 s, 60°C for 1 min, followed by 95°C for 15 s, 60°C for 30 s and 95°C for 15 s. Target gene levels were normalized to the housekeeping gene 18sRNA.

**Validation by immunostaining.** To detect the cellular localization and protein expression of type I collagen, the fibroblasts were grown in 35 mm dish and then treated under the indicated conditions. After fixing with 4% paraformaldehyde for 20 min and washed three times with PBS, the fibroblasts were permeabilized and blocked with 0.2% Triton-X and 1% normal goat serum (NGS) in phosphate-buffered saline (PBS) for 20 min at room temperature. Subsequently, the samples were incubated with primary antibody of type I collagen (1:300) overnight at 4°C. After the fibroblasts were washed three times with PBS, the fibroblasts were incubated with for Alexa Fluor 488 probe (1:500, Invitrogen, Carlsbad, CA) 1 h at RT in dark. The fibroblasts were mounted with DAPI (Dojundo) and imaged by using *in vitro* confocal microscope.

**Statistical analysis.** Data are expressed as mean ± SD. Differences between the mean values were analysed using the unpaired Student's *t* test: **p*<0.05; ***p*<0.01.

## Results

**$CoQ_{10}$ contents in fibroblasts.** $CoQ_{10}$ contents in fibroblasts were determined by HPLC-ECD with the method of Okamoto *et al.*[14] In this study, the fibroblasts were supplemented with P40 for a one week. Because, the aim of this study was to confirm whether $CoQ_{10}$ act only by intracellular $CoQ_{10}$ after being incorporated into a cell. The result showed that supplement of P40 also dose-dependently enhanced intracellular $CoQ_{10}$ level in fibroblasts (Fig. 1). Treatments of the same volume of control, i.e., placebo $CoQ_{10}$, in cultured fibroblasts have no affect intracellular $CoQ_{10}$ levels.

**Effect of P40 of proliferation in fibroblasts.** It is well known that decrease of cell proliferation is caused by aging or injury. Accordingly, decrease of cell proliferation participate in the aging of skin, and its improvement suggests the possibility of anti-aging effect in skin. The effect of P40 on the cell proliferation of fibroblasts were examined by MTT assay methods.[16] In this study, treatment of 1 μM P40 in fibroblasts has little effect on cell proliferation, whereas 10 μM P40 increased the number of fibroblasts (Fig. 2).

**The mRNA level of type I, IV, and VII collagens in fibroblasts.** The effect of P40 was examined by measuring mRNA level of collagens which is constituent of the dermis. The mRNA level was determined by methods of TaqMan with RT-PCR. P40 increased mRNA level of type I, IV, and VII collagens of fibroblasts in a dose-dependent manner. It also dose-dependently enhanced these mRNA levels of type I, IV, and VII collagens in fibroblasts (Fig. 3). On the other hand, treatment of

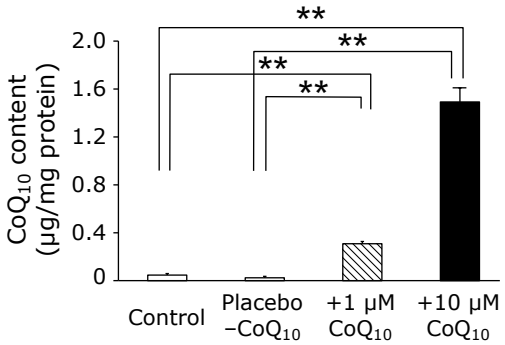


**Fig. 1.** The fibroblasts were cultured in the presence of P40 for a one week, after, intracellular $CoQ_{10}$ levels are determined by HPLC-ECD methods. Results are means ± SD. $n = 4–7$, **$p<0.01$.

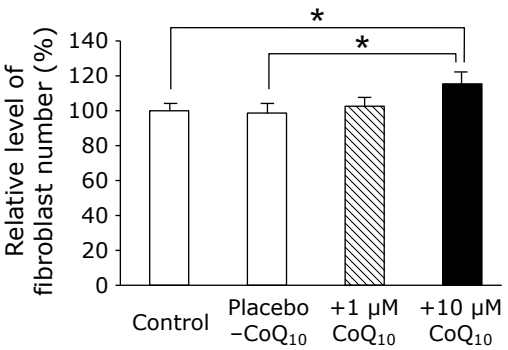


**Fig. 2.** Cell proliferation in fibroblasts were examined by MTT assay methods. The fibroblasts were treated with 10 μM P40, which increased the number of fibroblasts. Results are means ± SD. $n = 6$, *$p<0.05$.


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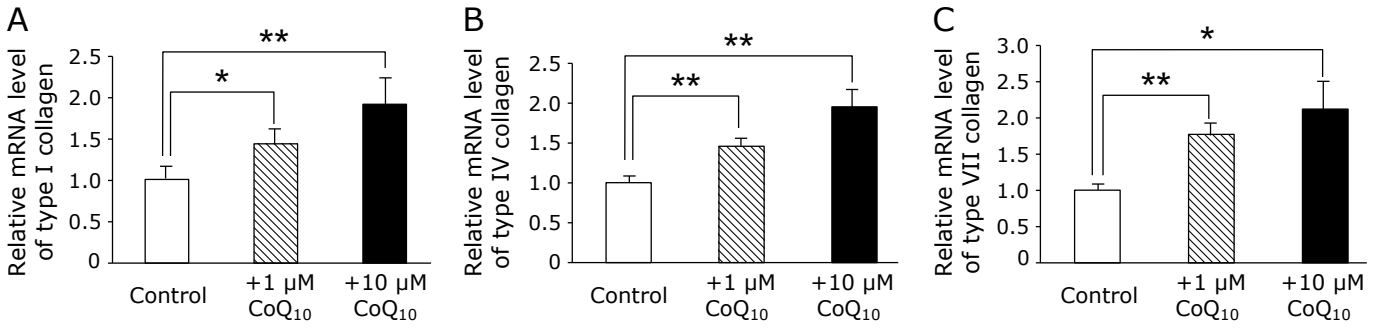


**Fig. 3.** Relative mRNA expression of type I, IV, and VII collagens were determined by RT-PCR method and the target gene levels were normalized to the housekeeping gene 18sRNA. (A) The mRNA level of type I collagen was increased by treatment of P40, and it also dose-dependently enhanced in fibroblasts. Results are means ± SD. $n = 3–7$, *$p<0.05$, **$p<0.01$. (B) A part of basement membrane is composed of type IV collagen, and it was increased to treatment of P40 in fibroblasts. Results are means ± SD. $n = 4–5$, **$p<0.01$. (C) Type VII collagen participate to connect basement membrane to dermis in skin. The fibroblasts were treated with more than 1 μM P40 increased mRNA levels of type VII collagen. Results are means ± SD. $n = 3$, *$p<0.05$, **$p<0.01$.

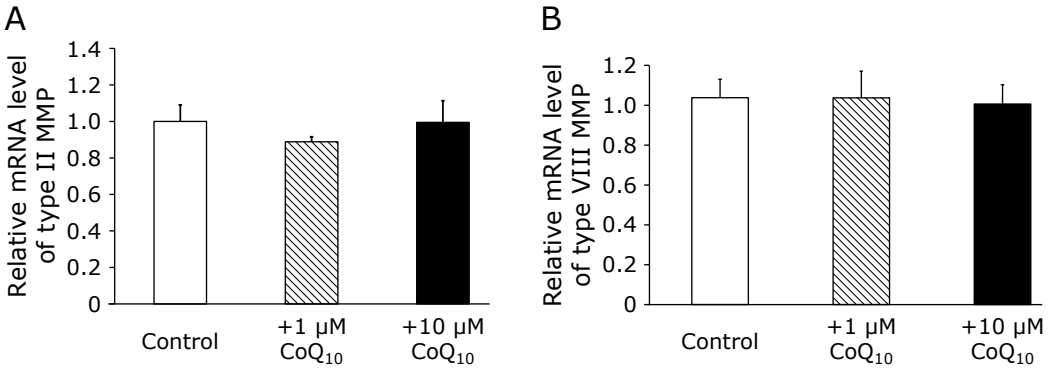


**Fig. 4.** Relative mRNA expression of type II and VIII MMP were determined by RT-PCR method and the mRNA levels of MMP were normalized to the housekeeping gene 18sRNA. (A) Type II MMP participate in the degradation of type IV and VII collagen. There was no significant difference in mRNA expression of type II MMP between treated of 1 or 10 μM P40 group and control group Results are means ± SD. $n = 3$. (B) Type I collagen is disassembled by type VIII MMP in skin. Treatment of P40 in fibroblasts showed that mRNA level of type VIII MMP were no longer significant compared with control group. Results are means ± SD. $n = 6$.

the same volumes of control, i.e., placebo $CoQ_{10}$, in cultured fibroblasts have no affect on mRNA levels of type I, IV, and VII levels.

**The mRNA level of type II and VIII MMP in fibroblasts.** MMP comprise a family of zinc-dependent endopeptidases that consist of more than 21 types MMP in human. In addition, MMP family has been known as catabolic enzyme of collagen. Type IV and VII collagen are degraded by type II MMP, and type I, II, and III collagen are degraded by type VIII MMP.[17] In this study, mRNA expression of type II and VIII MMP were measured by using RT-PCR with TaqMan methods. These results showed that there was no significant difference in mRNA expression of type II and VIII MMP between treated of P40 group and control group (Fig. 4).

**The mRNA level of HSP47 and elastin in fibroblasts.** The formation of mature collagen is associated with the expression of heat shock protein 47 (HSP47), and it is a collagen-specific chaperone that is essential for the triple helical formation in the endoplasmic reticulum.[18,19] Elastin is flexible and elastic fiber, which is structural protein capable of stretching in two dimensions. In the skin, both of HSP47 and elastin play an important role of physiological action, these are essential molecules for normal skin function. In this result show that P40 increased mRNA level of HSP47 and elastin of fibroblasts in a dose-dependent manner. It also dose-dependently enhanced these mRNA levels of HSP47 and elastin in fibroblasts (Fig. 5).

**Validation by immunostaining of collagen type I in fibroblasts.** Protein expression of type I collagen in fibroblasts were determined by immunofluorescence. Collagen molecules have three α-chain that form a triple helix, and it play an important role in skin functions. The role of type I collagen is well known to provide physical strength to tissue as the major components of ECM. These results showed that P40 increased collagen protein levels in skin fibroblasts (green fluorescence). (Fig. 6).

## Discussion

$CoQ_{10}$ is essential constituent components in mitochondrial respiratory chain, which play an important role of ATP synthesis and antioxidant effect. In Japan, $CoQ_{10}$ has been widely commercially available as a dietary and health supplement since 2001 and is used for the prevention of lifestyle-related diseases induced by free radicals and aging. Meanwhile, $CoQ_{10}$ in the bodies of human beings is thought to be provided by both dietary intake, such as dietary foods and health supplements, and *de novo* biosynthesis,[8] and $CoQ_{10}$ has a widespread distribution in human tissues, but the abundance of $CoQ_{10}$ are different between each tissue.[20–22] In particular, $CoQ_{10}$ levels in skin is very low compared with heart, liver, muscle and brain tissues. Consequently, it is assumed that exogenous $CoQ_{10}$ play an important role for skin functions. However, $CoQ_{10}$ is practically insoluble in water, thereby $CoQ_{10}$ having a low absorption property from the

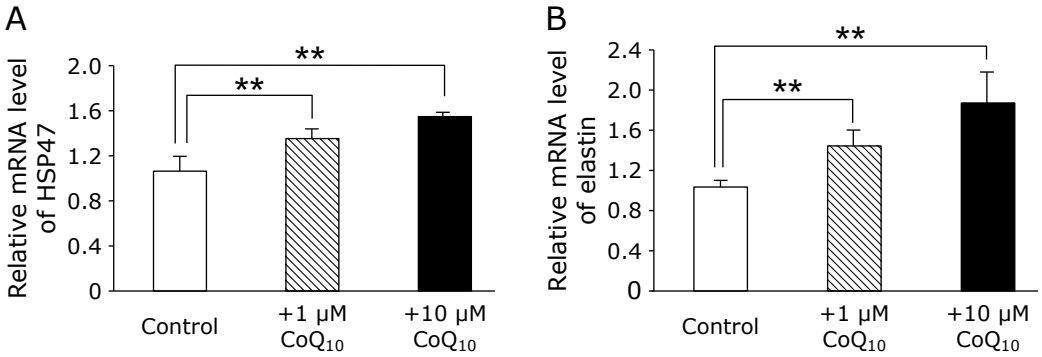


**Fig. 5.** Relative mRNA expression of HSP47 and elastin were determined by RT-PCR method and the target gene levels were normalized to the housekeeping gene 18sRNA. (A) The mRNA level of HSP47 was increased by treatment of P40, and it also dose-dependently enhanced in fibroblasts. Results are means ± SD. $n = 4–5$, $^{**}p<0.01$. (B) Treatment of P40 in fibroblasts showed to increase mRNA expression of elastin in a dose-dependent manner. Results are means ± SD. $n = 6$, $^{**}p<0.01$.

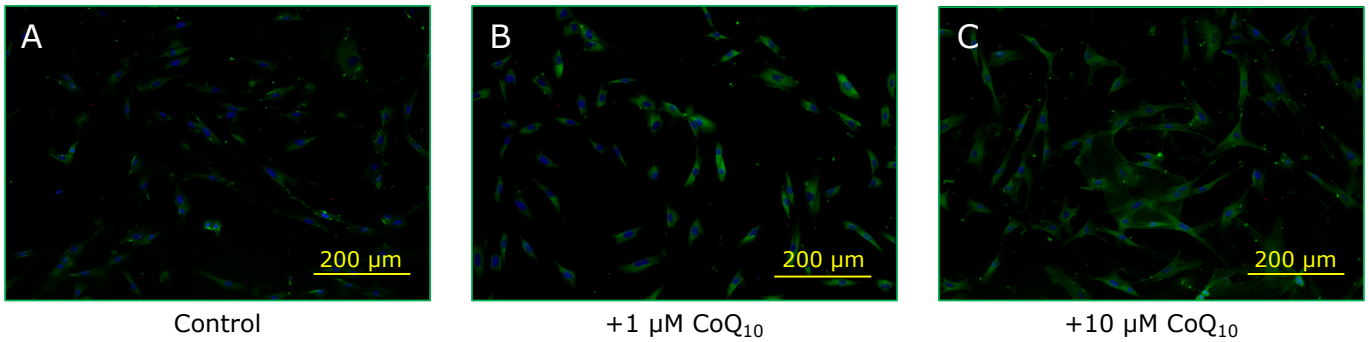


**Fig. 6.** Type I collagen protein expression in fibroblasts was determined by immunofluorescence, cell nuclei are stained blue with DAPI, and type I collagen protein is stained green with Alexa Fluor 488 probe. Scale bar shows 200 μm.

digestive tract and skin.

Recently, for the improvement of absorption, it has been developed the various $CoQ_{10}$ formulations (e.g. micellization,[23] water soluble,[24,25] and reduced form[26]). Then, it is possible that water soluble $CoQ_{10}$ (P40) indicate good absorption from the digestive tract and skin, and $CoQ_{10}$ levels in serum and skin increase compared with using lipid soluble $CoQ_{10}$. Besides, according to previous paper, low levels of $CoQ_{10}$ are found in several diseases[8] and the $CoQ_{10}$ level in the body has been reported to decrease after the age of 20 years.[27] Furthermore, it is well known that decrease of cell proliferation and collagen synthesis participate in the aging of skin, thus, we examined that effect of $CoQ_{10}$ in human skin fibroblasts. Before the addition of P40 in cultured fibroblasts, we attempted to dissolve $CoQ_{10}$ in ethanol or DMSO instead of P40. However, even though the concentration of 1 μM $CoQ_{10}$ dissolve in ethanol or DMSO, these solvents indicated toxic effects to fibroblasts.

In this study, intracellular $CoQ_{10}$ level increased by the addition of 1 or 10 μM P40, and 10 μM P40, and enhanced cell proliferation of skin fibroblasts. A number of studies with using lipid soluble $CoQ_{10}$ suggested that $CoQ_{10}$ has anti-aging effect in skin fibroblasts by increased type IV collagen expression and inhibition of UV-induced ROS and MMP-1 production.[9–11] Accordingly, after addition of P40 for 1 week, we confirmed on the expression level of collagen and MMP in fibroblasts by methods of TaqMan with RT-PCR. Like similarly to previous papers, mRNA expression of type IV and VII collagen were elevated by treatment of 1 or 10 μM P40 for 1 week.

However, P40 had no impact on mRNA expression of type II and VIII MMP that is known as a collagen degrading enzyme. These results suggested that P40 has been participating in collagen synthesis, it hasn't been involved in degradation of collagen in absence of ROS.

As mentioned above, $CoQ_{10}$ is confirmed to stimulate of type IV and VII collagen synthesis by addition P40 in skin fibroblasts, whereas interestingly, P40 increased type I collagen in this study. Previously studies[11,12] have shown that $CoQ_{10}$ had no effect on type I collagen production in fibroblasts. The reason is an unknown, however, we infer that there is different point of collagen synthesis mechanism between lipid soluble $CoQ_{10}$ and water soluble $CoQ_{10}$. Collagen is the most abundant protein in human body, constituting from 25% to 35% of the whole bodies protein content. Among the collagen types, type I collagen is the most ubiquitous and abundant in human body, and it is a typical fibril-forming collagen and a major component of the ECM. Therefore, effect of P40 is considered to very important by increase in synthesis of type I collagen in skin fibroblasts. A treatment of human skin fibroblasts with P40 induced mRNA level of elastin and HSP47. Elastin is flexible and elastic fiber, which is structural protein capable of stretching in two dimensions, and HSP47, participate in collagen maturation, are collagen-specific molecular chaperone that is essential for the triple helical formation.[28] Hence, not only increased production of collagen, P40 may play an important role in regulating physiological function according to increased expression mRNA of elastin and HSP47 in skin fibroblasts. Collagen and elastin are important fibrous protein of dermis to maintain normal skin structure and function. Accordingly, decrease of these fibrous proteins are known to be involved in formulation of wrinkle, which are accelerated by UVB and aging. In addition,


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Inui *et al.*[10] have reported that collagen is degradated via increasing MMP expression by UVB, and $CoQ_{10}$ inhibit the upregulation of MMP expression, thus $CoQ_{10}$ act on collagen to protect in presence of oxidative stress. Moreover, cell proliferation in skin fibroblasts is evoked by addition to $CoQ_{10}$, so that skin fibroblasts could more produce of collagen and elastin in dermis.

These results suggested that P40 has the efficacy that its increase collagen production of fibroblasts, thereby there is possible of the anti-aging by P40 in Japan which reached an aging society, so that it might be based on new physiological function by water soluble $CoQ_{10}$.

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## Conflict of Interest

No potential conflicts of interest were disclosed.

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*antioxidants*

MDPI

*Review*

# Coenzyme $Q_{10}$: Clinical Applications in Cardiovascular Diseases

**Alma Martelli [1,2,3,†], Lara Testai [1,2,3,†], Alessandro Colletti [4,5] and Arrigo F. G. Cicero [5,6,*]**

1 Department of Pharmacy, University of Pisa, 56120 Pisa, Italy; alma.martelli@unipi.it (A.M.); lara.testai@unipi.it (L.T.)
2 Interdepartmental Research Centre "Nutraceuticals and Food for Health (NUTRAFOOD)", University of Pisa, 56120 Pisa, Italy
3 Interdepartmental Research Centre of Ageing, Biology and Pathology, University of Pisa, 56120 Pisa, Italy
4 Department of Science and Drug Technology, University of Turin, 10125 Turin, Italy; alessandro.colletti@unito.it
5 Italian Nutraceutical Society (SINut), Via Guelfa 9, 40138 Bologna, Italy
6 Medical and Surgical Sciences Department, University of Bologna, 40126 Bologna, Italy
* Correspondence: arrigo.cicero@unibo.it; Tel.: +39-512142224
† These authors contributed equally to this work.

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**Abstract:** Coenzyme $Q_{10}$ ($CoQ_{10}$) is a ubiquitous factor present in cell membranes and mitochondria, both in its reduced (ubiquinol) and oxidized (ubiquinone) forms. Its levels are high in organs with high metabolism such as the heart, kidneys, and liver because it acts as an energy transfer molecule but could be reduced by aging, genetic factors, drugs (e.g., statins), cardiovascular (CV) diseases, degenerative muscle disorders, and neurodegenerative diseases. As $CoQ_{10}$ is endowed with significant antioxidant and anti-inflammatory features, useful to prevent free radical-induced damage and inflammatory signaling pathway activation, its depletion results in exacerbation of inflammatory processes. Therefore, exogenous $CoQ_{10}$ supplementation might be useful as an adjuvant in the treatment of cardiovascular diseases such as heart failure, atrial fibrillation, and myocardial infarction and in associated risk factors such as hypertension, insulin resistance, dyslipidemias, and obesity. This review aims to summarize the current evidences on the use of $CoQ_{10}$ supplementation as a therapeutic approach in cardiovascular diseases through the analysis of its clinical impact on patients' health and quality of life. A substantial reduction of inflammatory and oxidative stress markers has been observed in several randomized clinical trials (RCTs) focused on several of the abovementioned diseases, even if more RCTs, involving a larger number of patients, will be necessary to strengthen these interesting findings.

**Keywords:** coenzyme $Q_{10}$; ubiquinone; cardiovascular disease; risk factors; prevention; supplementation

## 1. Introduction

Coenzyme $Q_{10}$ ($CoQ_{10}$) is an organic molecule that was identified for the first time by Frederick Crane of Wisconsin (USA) in 1957 [1]. It is ubiquitously present in cell membranes and especially in the mitochondria in both reduced (ubiquinol) and oxidized (ubiquinone) forms (Figure 1). Chemically, it is constituted of a benzoquinone group and a poly-isoprenoid side chain that is species specific. In the human, it is composed of 10 units and called $CoQ_{10}$ or ubiquinone [2]. This molecule can sustain continuous oxidation–reduction cycles and is an excellent electron carrier. $CoQ_{10}$ concentration is particularly high in organs such as the kidneys, heart, and liver (Table 1) because they need it as an efficient energy transfer molecule supporting their high metabolic rate [3].

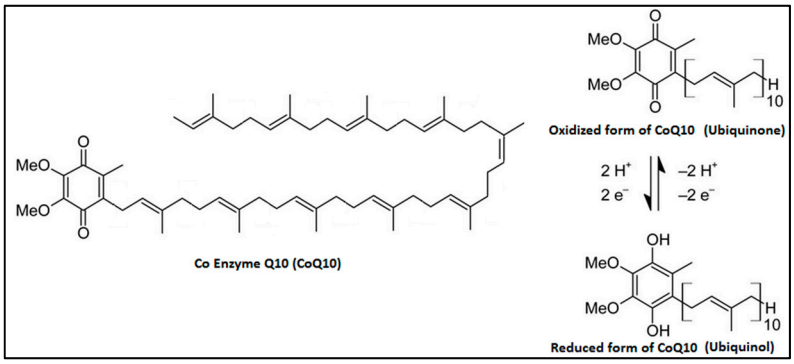


**Figure 1.** Chemical structure of $CoQ_{10}$.

**Table 1.** Distribution of ubiquinone and ubiquinol in human tissues (modified from References [4,5]).

| Organ | Ubiquinone Concentration (μg/g) | Ubiquinol Concentration (μg/g) |
|---|---|---|
| Heart | 132.0 | 61.0 |
| Kidneys | 77.0 | 75.0 |
| Liver | 63.6 | 95.0 |
| Muscle | 39.7 | 65.0 |
| Brain | 13.4 | 23.0 |
| Pancreas | 32.7 | |
| Spleen | 24.6 | |
| Lung | 7.9 | 25.0 |
| Thyroid | 24.7 | |
| Testis | 10.5 | |
| Intestine | 11.5 | 95.0 |
| Colon | 10.7 | |
| Ventricle | 11.8 | |
| Plasma (μmol/mL) | 1.1 | 96.0 |

Physiologically, $CoQ_{10}$ is anchored in the cell membrane through the isoprenoid tail, whereas the benzoquinone ring moves in the membrane based on its redox state. The most prominent role of $CoQ_{10}$ is to facilitate the production of ATP through participation in the electron transport chain in the mitochondria. In fact, in the respiratory chain, $CoQ_{10}$ transfers electrons from complex I (nicotinamide-adenine dinucleotide (NADH)-coenzyme Q reductase) or complex II (succinate-coenzyme Q reductase) to complex III (cytochrome c reductase), and it is also a structural component of both CI and CIII, reducing the production of reactive oxygen species (ROS) [6,7].

Moreover, $CoQ_{10}$ is able to accept electrons from fatty acyl-coenzyme A (acyl-CoA) dehydrogenases and it is an obligatory factor in proton transport by uncoupling proteins (UCPs), thus regulating the opening of mitochondrial permeability transition pores [8]. Other functions of $CoQ_{10}$ in the cell membrane include stabilization of calcium-dependent channels, metabolic regulation, cell signaling, and cell growth through local regulation of cytosolic redox intermediates such as dihydronicotinamide-adenine dinucleotide phosphate (NADPH) [6].

$CoQ_{10}$, in its reduced form, has been shown to inhibit the peroxidation of cell membrane lipids and to reduce the oxidation of circulating lipids. Interestingly, in vitro, it inhibits the oxidation of low-density lipoprotein more than other antioxidant molecules, such as α-tocopherol or β-carotene [9,10].

$CoQ_{10}$ is mostly synthetized in the cell, although the pathway involved is not yet completely known. A biosynthetic complex for producing $CoQ_{10}$, containing proteins, lipids, and polar small molecules

(but with specific composition unknown), was recently revealed in yeast and mammals. In particular, multiple mitochondrial uncharacterized proteins (MXPs) have been linked to $CoQ_{10}$ biosynthesis and recent progress was made also toward understanding the biochemistry of a dehydrogenase, a deaminase, a lipid-binding protein, and a protein kinase-like enzyme in the $CoQ_{10}$ pathway [11]. In mammalians, 4-hydroxybenzoate is the precursor of the quinone ring, derived from tyrosine, while the isoprenoid tail is derived from the mevalonate pathway, using the common way with cholesterol biosynthesis. The final step, rate limiting, occurs in the mitochondrial matrix [12,13].

On the other hand, $CoQ_{10}$ can be derived from the diet; in particular, fatty fish (salmon, sardin, and tuna), soya, spinach, and nuts contain high levels of this cofactor. However, the intake from the diet is significant only in deficiency conditions [14]. Some factors may reduce plasma concentrations of $CoQ_{10}$, such as aging, genetic factors, drugs (e.g., statins), certain diseases (e.g., cardiovascular disease and degenerative muscle disorders), and increased demand [15].

Therefore, it is not surprising that its depletion is associated with a greater propensity to develop immune inflammatory responses through the activation of inflammatory processes such as the nuclear factor-kappa-light-chain-enhancer of activated B cell's (NF-κB) gene expression [16]. Worthy to note, $CoQ_{10}$ is endowed with potent antioxidant action able to prevent free radical damage by the regulation of transcriptional pathways in addition to deactivation of inflammatory pathways [17]. Therefore, supplementation with $CoQ_{10}$ could be efficient in the prevention and/or treatment of a number of pathogenic disorders in relation to the significant reduction of inflammatory markers [18].

Due to its important place in organisms' functioning, there are many diseases and degenerative states associated with $CoQ_{10}$'s deficiency, such as cardiovascular disease, muscular dystrophy, Alzheimer's disease, Parkinson's disease, and others [7]. However, if on the one hand clinical evidences in the cardiovascular field have demonstrated the potential role of $CoQ_{10}$, data concerning the supplementation of this nutraceutical in neurodegenerative diseases and other conditions such as cancer or muscular dystrophy are often old and still conflicting and need additional randomized controlled trials (RCTs) [19–21].

This review aims to sum up the current possibilities to use $CoQ_{10}$ as an adjuvant in cardiovascular disease-affected patients, in cardiovascular disease risk factors, and in statin-intolerant ones, with an analysis of its impact on patients' health and quality of life.

## 2. Methods

A systematic search strategy was conducted for this review in order to identify trials in both the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK) and MEDLINE (National Library of Medicine, Bethesda, Maryland, MD, USA; January 1970 to March 2020). The terms "coenzyme $Q_{10}$", "dietary supplement", "ubiquinol", "ubiquinone", "clinical trial", and "human" were incorporated in an electronic search strategy. Overall, we screened 5278 abstracts. The selected references were then further screened for application on cardiovascular diseases or cardiovascular disease risk factors. After a general introduction with an overview on the pharmacodynamic profile of $CoQ_{10}$, for each potential therapeutic indication, a short description of the mechanism of action has been reported, followed by the clinically observed effects and the most relevant tolerability notes. The authors of the writing and reviewing panels completed *Declaration of Interest* forms where real or potential sources of conflicts of interest might be perceived.

## 3. Results

This review will focus our attention on the main potential evidence-based use of $CoQ_{10}$ supplements in the management of some main cardiovascular disease risk factors and of cardiovascular disease-affected patients and in statin-intolerant ones (Figure 2).

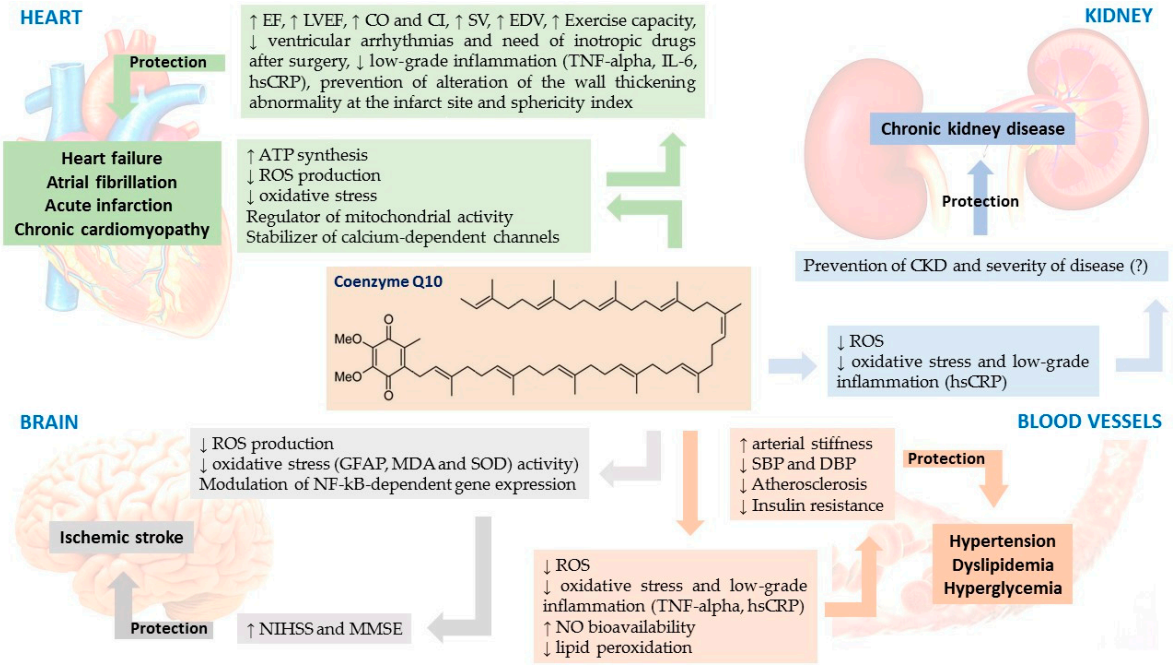


**Figure 2.** Involvement of $CoQ_{10}$ deficiency and cardiovascular disease risk factors. ATP: adenosine triphosphate; CI: cardiac input; CO: cardiac output; CKD: chronic kidney disease; DBP: diastolic blood pressure; EDV: end-diastolic volume; EF: ejection fraction; GFAP: glial fibrillary acidic protein; hs-CRP: high sensible- C reactive protein; IL-6: interleukin-6; LVEF: left ventricular ejection fraction; MDA: malondialdehyde; mmSE: mini mental state examination; NIHSS: national institute of health stroke scale; NO: nitric oxide; NF-kB: nuclear factor kappa B; ROS: reactive oxygen species; SBP: systolic blood pressure; SOD: superoxide dismutase; SV: stroke volume; TNF-alpha: tumor necrosis factor-alpha.

### *3.1. $CoQ_{10}$ and Cardiovascular Risk Factors*

As stated above, $CoQ_{10}$ supplementation could find a role in the management of some highly prevalent cardiovascular and cerebrovascular disease risk factors, such as high blood pressure, insulin resistance, dyslipidemia, migraine, and chronic kidney disease.

#### 3.1.1. High Blood Pressure

Hypertension is one of the major causes of morbidity and mortality worldwide, involving one in four men and one in five women, totalling 1.13 billion adults, who had raised blood pressure in 2015 [22]. A recent comparative assessment of the risk of health loss related to systolic blood pressure (SBP), based on 844 studies in 154 countries (published between 1980 and 2015) and 8.69 million participants, has estimated approximately 874 million of people in the world with SBP above 140 mmHg [23]. In 2025, it is estimated that there will be approximately 1.56 billion hypertensive adults [24].

$CoQ_{10}$ seems to exert a direct effect on the endothelium, provoking vasodilation and lowering blood pressure [25,26]. This effect is linked to its ability to improve nitric oxides bioavailability and to induce vasodilatation especially in patients with hypertension. In addition, $CoQ_{10}$ adjusts the angiotensin effect in sodium retention and decreases the level of aldosterone [27,28]. Despite exciting blood pressure results observed in preliminary trials (systolic and diastolic blood pressure reduced respectively by 6 and 5 mmHg vs. placebo) [29] and the positive results confirmed by old meta-analyses of RCTs [30,31], a recent meta-analysis of 17 randomized controlled trials including 684 subjects showed that $CoQ_{10}$ supplementation significantly decreased systolic blood pressure (Standardized Mean Difference (SMD) −0.30; 95%CI −0.52, −0.08), but not diastolic blood pressure (SMD −0.08; 95%CI −0.46, 0.29) [32]. However, in patients with type 2 diabetes mellitus and ischemic left ventricular systolic dysfunction, when the blood pressure is on target, the supplementation of $CoQ_{10}$ did not modify the

blood pressure [33–35]. In conclusion, despite some promising evidence, the antihypertensive effect of $CoQ_{10}$ is still unclear in patients with primary hypertension [36,37].

#### 3.1.2. Insulin-Resistance and Type 2 Diabetes

Mitochondria seem to play a key role in the development of insulin resistance. They are well known to convert nutrients from diet such as fats and sugars into ATP; however, ATP production can generate harmful intermediates such as ROS and the increase in the amount of oxidant agents produced in mitochondria has been linked to the increase of insulin resistance [38,39]. Several studies in vitro and in vivo as well [40] found that the concentrations of $CoQ_{10}$ were lower in mitochondria from insulin-resistant fat and muscle tissue, probably for a change in expression of mevalonate/$CoQ_{10}$ pathway proteins and thus altered $CoQ_{10}$ metabolism, suggesting a direct correlation between the low levels of $CoQ_{10}$ and the high levels of oxidants in the mitochondria. In addition, the administration of $CoQ_{10}$ in deficient and insulin resistant mice has been shown to improve the insulin sensitivity by reducing ROS levels [40].

In patients with metabolic syndrome (MetS), a condition typically caused by insulin-resistance and strongly associated with the risk to developing cardiovascular disease, the intake of 100 mg/day of $CoQ_{10}$ for 8 weeks significantly improved Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Homeostatic Model Assessment of β-cell Function (HOMA-B), serum insulin levels, and plasma total antioxidant capacity [41]. The effect of $CoQ_{10}$ on insulin-resistance seems to not be related to its effect on body fat. In fact, a recent meta-analysis of RCTs showed that $CoQ_{10}$ had no significant impact on body weight ($p = 0.64$) and body mass index (BMI) ($p = 0.86$), independent from the $CoQ_{10}$ tested dosage and trial duration [42].

Another highly prevalent cardiovascular risk factor related to insulin-resistance is nonalcoholic fatty liver disease (NAFLD) [43]. Despite the numerous mechanisms investigated, the exact biological one related to increased hepatic inflammation and fat accumulation in NAFLD remains largely unknown [44,45]. However, recent studies have focused attention on the role of mitochondrial protein mitofusin 2 (Mfn2) that protects against liver disease. In fact, reduced Mfn2 expression was detected in liver biopsies from patients with nonalcoholic steatohepatitis [46]. The loss of Mfn2 seems to impair mitochondrial respiration and to reduce ATP production, and this defective oxidative phosphorylation process seems to unexpectedly originate from a depletion of the mitochondrial $CoQ_{10}$ pool [47].

To date, the treatment of NAFLD is essentially based on lifestyle optimization because there are currently no specific drugs approved on the market for this condition. At the same time, few nutraceuticals have been adequately studied for their effects on NAFLD [48]. Among these, $CoQ_{10}$ is a well-known anti-adipogenic molecule and thus could have a positive impact on NAFLD, even if its exact mechanism is still unclear. It is possible that $CoQ_{10}$ downregulates the expression of fatty acid synthase (FAS), sterol regulatory element-binding protein-1c (SREBP-1c), and acetyl-CoA carboxylase (ACC), which are related to lipid synthesis, and increases in the expression of carnitine palmitoyltransferase-1 (CPT-1) and peroxisome proliferator-activated receptors α (PPARα) associated with fatty acid oxidation [49]. In addition, $CoQ_{10}$ could change the response to inflammation through nuclear factor kappa B (NF-kB)-dependent gene expression [50]; thus, its deficiency might have a role in increasing levels of inflammatory molecules like NF-kB [51].

$CoQ_{10}$ could serve as an adenosine monophosphate-activated protein kinase (AMPK) activator and could regulate the hepatic lipid metabolism to inhibit the abnormal accumulation of hepatic lipids as well as to prevent NAFLD progression [49]. Finally, $CoQ_{10}$ was also found to bind and activate both PPARs alpha and gamma, suggesting a key role in relaying the states of mitochondria and peroxisomes [52]. At the same time, the experiments performed with peroxisomal inducers indicate that nuclear receptors are involved in the regulation of $CoQ_{10}$ biosynthesis [13].

In an RCT, 41 subjects with NAFLD were randomly divided into 2 groups to receive $CoQ_{10}$ (100 mg/day) or placebo for 12 weeks. At the end of the study, the active group benefited from a significant decrease in aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT),

tumor necrosis factor α, high-sensitivity C-reactive protein (hs-CRP), and NAFLD grade compared to placebo ($p < 0.05$ for all). In addition, patients who received the $CoQ_{10}$ supplement had higher serum levels of adiponectin ($p = 0.016$) even if serum leptin levels reduced marginally ($p = 0.053$) [53]. However, $CoQ_{10}$ administration (300 mg/day for 12 weeks) in patients with coronary artery disease did not find any significant effect on serum adiponectin levels [54], confirming previous data obtained by Gokbel et al. with the supplementation of $CoQ_{10}$ 100 mg/day in healthy volunteers [55]. In another RCT, the same dose of $CoQ_{10}$ in 44 NAFLD patients for 4 weeks was associated with significantly decreased waist circumference (WC), serum AST, and total antioxidant capacity (TAC) concentration ($p < 0.05$ for all) [56].

$CoQ_{10}$ could also improve the atherogenic dyslipidemia typically associated with NAFLD (reducing triglycerides (TG) and increasing high-density lipoprotein cholesterol (HDL-C) as well as reduce oxidized low-density lipoprotein (LDL) levels and arterial pressure with a very high safety profile and without any risk of drug interactions [15]. In conclusion, the studies conducted to date emphasize a potential for $CoQ_{10}$ therapy in improving several anthropometric and biochemical variables in NAFLD.

A further disease typically characterized by insulin resistance is polycystic ovary syndrome (PCOS). In these women, as showed by the study of Samimi et al., the supplementation with $CoQ_{10}$ (100 mg/day) for 12 weeks could have beneficial effects on glucose metabolism and on serum total- and LDL-cholesterol levels [57]. Afterwards, the same research group carried out another RCT on 40 women with a diagnosis of PCOS, observing that a supplementation for 12 weeks with $CoQ_{10}$ (100 mg/day), beside the positive effects on lipid and glucose levels, was responsible for a downregulation of gene expression of oxidized low-density lipoprotein (LDL) receptor 1 ($p < 0.001$) and an upregulated gene expression of PPAR-γ ($p = 0.01$) in peripheral blood mononuclear cells. In addition, compared to the placebo group, $CoQ_{10}$ supplementation downregulated gene expression of interleukin-1 (IL-1) ($p = 0.03$), IL-8 ($p = 0.001$), and tumor necrosis factor-alpha (TNF-α) ($p < 0.001$) in peripheral blood mononuclear cells of subjects with PCOS [58]. Similar results were obtained by Izadi et al. in a RCT of 85 PCO women treated with $CoQ_{10}$ and/or vitamin E or placebo. In particular, $CoQ_{10}$ alone improved the sex homone profile, specially either reduced testosterone and luteinizing hormone (LH) levels, and improved insulin resistence. Moreover, it is noteworthy that $CoQ_{10}$ in coadministration with alfa-tocopherol presented a more pronunced effect and stimulated the release of sex hormone-binding globulin (SHBG), justifing the enhancement of insulin tolerance, since an insulin resistance condition is associated with a reduced synthesis of SHBG at the hepatic level. Then, $CoQ_{10}$ might promote steroid hormone biosynthesis and normal reproductive function (among which are oocyte maturation, fertilization, and embryonic development) through the improvement of mitochondrial functionality [59]. However, new, larger RCTs are needed to confirm the results obatined by Izadi et al.

The extreme consequence of insulin-resistance is Type 2 diabetes (T2DM). A deficiency of $CoQ_{10}$ plasma levels in patients with T2DM can be observed compared to healthy people [60,61]. In particular, the ubiquinone–ubiquinol ratio, a validated marker of oxidative stress [62], is much higher in a patient with T2DM after breakfast and throughout the day, which suggests heightened oxidative stress in the background of postprandial hyperglycemia [63]. In a recent pooled analysis of 14 trials including 693 overweight diabetic patients, $CoQ_{10}$ interventions significantly reduced fasting plasma glucose (FPG) (−0.59 mmol/L; 95%CI −1.05 to −0.12; $p = 0.01$), HbA1c (−0.28%; 95%CI −0.53 to −0.03; $p = 0.03$), and TG levels (0.17 mmol/L; 95%CI −0.32 to −0.03; $p = 0.02$). Even in the subgroup analysis, the low-dose consumption of $CoQ_{10}$ (<200 mg/d) effectively reduced the values of FBG, HbA1c, fasting blood insulin, homeostatic model assessment for insulin resistance (HOMA-IR), and TG with high tolerability profile [64]. In a rat model, the administration of metformin combined with $CoQ_{10}$ showed a better renoprotective effect than $CoQ_{10}$ or metformin alone [65]. This is also confirmed for other oral antidiabetic drugs like sitagliptin [66]. This brings up an important point that $CoQ_{10}$ may potentiate the protective effects of some conventional treatments, but it is yet to be demonstrated in humans.

#### 3.1.3. Dyslipidemias

Several mechanisms have been proposed by which $CoQ_{10}$ supplements could improve metabolic profiles which probably might be through the induction of gene expression of PPAR-γ [67], a nuclear receptor protein that regulates gene expression involved in insulin and lipid metabolism, differentiation, proliferation, survival, and inflammation [68]. In human endothelial cells, the exposure to $CoQ_{10}$ is associated with downregulation of the lectin-like oxidized LDL receptors, stimulation of the AMPK, and reduction of the ROS-induced endothelial damage [69]. In fact, the main effect of $CoQ_{10}$ on plasma lipids seems to be the increased LDL resistance to oxidative stress [70], as also demonstrated in healthy adults after acute strenous physical exercise [71].

In an RCT, 101 dyslipidemic subjects without taking any lipid-lowering drugs were administrated 120 mg $CoQ_{10}$ or placebo daily for 24 weeks. At the end of the study, $CoQ_{10}$ supplementation mildly reduced TG ($p = 0.020$) and LDL-C ($p = 0.016$), increased apolipoprotein (Apo)A-I ($p < 0.001$) and serum total antioxidant capacity (TAC; $p = 0.003$), while decreased homeostasis model assessment of insulin resistance index ($p = 0.009$) compared to placebo [24]. In the meta-analysis conducted by Sharifi et al. [72], $CoQ_{10}$ administration to patients with metabolic diseases mildly but significantly reduced TG concentrations (SMD −0.28 mmol/L; 95% CI, −0.56 to −0.005, $p = 0.001$). A recent meta-analysis including six clinical trials suggests that $CoQ_{10}$ could mildly reduce the lipoprotein (a) plasma level [73]. Overall, the effect of $CoQ_{10}$ supplementation on plasma lipid levels is, however, quantitatively small and its clinical relevance has yet to be demonstrated.

#### 3.1.4. Systemic Inflammation

Inflammation is considered a main process involved in atherosclerosis development [74]. A recent meta-analysis of nine RCTs and 509 patients showed that the $CoQ_{10}$ supplementation in chronic inflammatory diseases (60–500 mg/day for 8–12 weeks) is responsible for the significant reduction in the plasma levels of tumor necrosis factor alpha (TNF-α) (SMD: −0.44, 95% CI: (−0.81 to −0.07) mg/dl; $I^2$ = 66.1%, $p < 0.01$) and in IL-6 levels (SMD: −0.37, 95% CI: (−0.65 to −0.09), $p = 0.01$) [75]. Similar results were obtained by the metanalysis of Fan et al. that demonstrated a reduction of the C-reactive protein levels in addition to the abovementioned parameters in patients afflicted by inflammatory diseases [76]; in elderly people with low $CoQ_{10}$ levels; and in patients with metabolic diseases characterized by chronic, low grade inflammation [17]. However, the results are conflicting while not so evident in patients affected by metabolic syndrome [41] and dyslipidemia [29].

### *3.2. $CoQ_{10}$ and Cardiovascular Disease*

$CoQ_{10}$ supplementation has been tested in a number of overt cardiovascular diseases, with the aim to evaluate its impact on self-perceived quality of life, instrumental parameters, and sometimes clinical outcomes as well.

#### 3.2.1. $CoQ_{10}$ and Heart Failure (HF)

HF is defined by the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood" [77,78]. It affects 23 million people worldwide [79], and the HF prevalence in the USA is 5 million people [80]. At the same time, this disease is also the main component for disability and hospitalization in the elderly and it is the cause of one in nine deaths in the USA [1]. In Europe, the prevalence and incidence of HF and the related costs are quite similar [81,82]. Despite that, in the last decades, the prevention and treatment of HF have improved significantly, quality of life is often impaired, and mortality rates are greater than 10% per year, reaching 20%–50% in more serious patients [83]. In the last years, a number of clinical studies have investigated the possibility that $CoQ_{10}$ can contribute to the prevention of incident HF and to the improvement of related symptoms and instrumental parameters. Being an essential

cofactor of the mitochondrial respiratory chain used for production of adenosine triphosphate (ATP), it is not surprising that the highest concentration compared to other tissues is focused on myocardium mitochondria [84].

A relative tissue $CoQ_{10}$ deficiency could then play an etiopathogenic role in the development and progression of HF: some evidence suggests that the depletion of $CoQ_{10}$ is proportional to the reduction of $CoQ_{10}$ myocardial tissue concentrations and to the severity of the disease developed [85–87]. In fact, the lowest levels of myocardial $CoQ_{10}$ have been observed in patients of New York Heart Association (NYHA) class IV compared to patients of NYHA class I [88,89]. Of course, one of the most important studies in the field of nutraceuticals, the Q-SYMBIO multicentre, randomized placebo-controlled trial, was used to assess the impact of the daily intake of $CoQ_{10}$ on total mortality and not just on the surrogate endpoints. Patients with moderate or severe HF currently treated with the pharmacological gold standard treatments (420 patients) were randomized to a daily intake of 300 mg of $CoQ_{10}$ ($n$ = 202) or placebo ($n$ = 218). After two years, a significant reduction in Major Adverse Cardiac Events (MACE) rate (15% in the $CoQ_{10}$ group vs. 26% in the placebo group, HR: 0.50; 95%CI: 0.32 to 0.80; $p$ = 0.003), CV mortality (9% vs. 16%, $p$ = 0.026), all-cause mortality (10% vs. 18%, $p$ = 0.018), and incidence of hospital stays for HF ($p$ = 0.033) were registered in $CoQ_{10}$-treated patients vs. the placebo treated ones [90]. This result was confirmed in a subsequent meta-analysis of 14 RCTs including 2149 patients. It has shown that administration of $CoQ_{10}$ reduces mortality (RR= 0.69; 95%CI: 0.50–0.95; $p$ = 0.02; $I^2$= 0%) and improves exercise capacity (SMD = 0.62; 95%CI: 0.02–0.30; $p$ = 0.04; $I^2$= 54%) compared to the placebo. However, no significant difference was observed in the endpoints of left ventricular ejection fraction (LVEF) between "active group" and placebo (SMD = 0.62; 95% CI: 0.02–1.12; $p$ = 0.04; $I^2$ = 75%) [91]. The effect on LVEF could be more relevant in patients with preserved ejection fraction (EF) [92] (net change: 4.8% vs. subjects with EF < 30%) and patients untreated with statins and/or angiotensin converting enzyme inhibitors (ACEi) (+6.7%) compared to the subgroup of patients treated with these drugs (+1.2%) [93]. One of the possible explanations of the heterogeneity in results on EF may be the diversity of $CoQ_{10}$ supplemented through different pharmaceutical forms and dosages. In fact, plasma concentrations of this molecule are extremely variable in relation to pharmaceutical form and administered dosages but were reported in few RCTs [94–96]. In addition, the diversity of HF grade of patients enrolled (NYHA I-II-III-IV), duration of treatments, and cotreatment with conventional therapies might be other factors that could explain the heterogeneity of results about EF [97].

### 3.2.2. $CoQ_{10}$ and Myocardial Infarction

HF could be related to different causes: one of the most frequent is ischemic damage. As highlighted before, treatment with $CoQ_{10}$ in HF could prevent myocardial cell damage and could restore tissue $CoQ_{10}$ deficiency, especially in myocardial tissue, with the final result being significant improvement in HF [98–101]. The degree of deficiency of this molecule has also been found to correlate directly with the degree of impairment in left ventricular function [102]. For these reasons, another possible indication of $CoQ_{10}$ supplementation is acute myocardial infarction (AMI). In fact, $CoQ_{10}$ is an ATP-sparing agent and regenerable antioxidant capable of protecting cell structures from oxidative damage during ischemia and reperfusion injury [103,104].

AMI is typically characterized by complications such as left ventricular dysfunction related to necrosis and loss of functioning myocardium and consequently by pathological remodelling, which seem to be related to reperfusion-induced free radical damage, lipid peroxidation, and decreased energy production and thus the lack of $CoQ_{10}$ [105–108]. Cardiac remodelling may be defined as "a group of molecular, cellular, and interstitial alterations that manifest clinically as changes in size, mass, geometry, and function of the heart after injury" [105]. These structural changes in ventricular remodelling in conjunction to tissue $CoQ_{10}$ deficiency may result in poor prognosis for its negative association with HF, which is the major cause of morbidity and mortality in patients with AMI [109]. *O*xidative stress may be important in the pathogenesis of remodelling which may begin via subcellular

remodelling leading to HF [110]. Therefore, any agent which can prevent remodelling in patients with AMI would be an important therapeutic aid for prevention of complications altering AMI [111,112]. In a recent RCT of 55 patients with LVEF < 50% after AMI, the effects of $CoQ_{10}$ (120 mg/day) or placebo were studied for 24 weeks. The results revealed that wall thickness opposite the site of infarction decreased from 12.2 ± 2.0 mm to 10.0 ± 1.8 mm with $CoQ_{10}$ compared with 12.8 ± 2.2 mm to 13.3 ± 2.3 mm with the placebo ($p < 0.01$). Left ventricular mass changed from 236 ± 72 g to 213 ± 61 g with $CoQ_{10}$ compared with 230 ± 77 g to 255 ± 86 g with placebo ($p < 0.01$). In addition, treatment with $CoQ_{10}$ also prevented alteration of the sphericity index (from 1.61 ± 0.28 to 1.63 ± 0.30 with $CoQ_{10}$ compared with 1.61 ± 0.32 to 1.41 ± 0.31 with placebo ($p < 0.05$)) and alteration of the wall thickening abnormality at the infarct site (from 9.4 ± 3.0 $cm^2$ to 9.1 ± 2.8 $cm^2$ compared with 10.1 ± 3.1 to 13.7 ± 4.2 $cm^2$ with placebo ($p < 0.05$)). Finally, end diastolic and systolic volumes and serum ACE also showed significant reduction with $CoQ_{10}$ compared to the control group [107]. The findings suggest that $CoQ_{10}$ administered early after AMI may be protective against left ventricular remodelling in patients with persistent left ventricular dysfunction. However, long-term RCTs are needed to confirm preliminary data.

#### 3.2.3. $CoQ_{10}$ and Atrial Fibrillation

Atrial fibrillation (AF) is considered a frequent atrial arrhythmia in patients diagnosed with HF or ischemic heart disease, and its prevalence has been growing worldwide in the last years. It is associated with an increase in morbidity and mortality [113–115]. As underlined for HF, $CoQ_{10}$ plays an important role in the production of ATP and its bioenergetic function associated to with antioxidant and scavenge ROS function which is essential for proper heart functioning [116,117]. A meta-analysis of eight RCTs found that patients treated with $CoQ_{10}$ were significantly less likely to develop ventricular arrhythmias (OR (95% CI) 0.05 (0.01–0.31)) and to require inotropic drugs after surgery (OR 95% CI 0.47 (0.27–0.81)). Twelve patients (22.2%) in the control group and three patients (6.3%) in the $CoQ_{10}$ group had episodes of AF after 12 months of treatment ($p = 0.02$). [118] Similar results were obtained by other authors, concluding that $CoQ_{10}$ as adjuvant treatment in patients with HF may attenuate the incidence of AF. The exact mechanisms of the effect are still unclear, even if one of the possible explanations could be attributed to the reduction of serum levels of malondialdehyde (MDA) [119].

#### 3.2.4. $CoQ_{10}$ and Nonischemic Cardiomyopathies

Cardiomyopathies are a number of debilitating conditions responsible for poor quality of life and high risk of mortality. Both in vitro and animal studies suggest a link between cardiomyopathies and oxidative stress [120]. $CoQ_{10}$ deficiency appears to be frequent in people with dilated cardiomyopathy, and its supplementation may be able to restore plasmatic and myocardial levels [121]. However, new studies are needed to confirm this evidence.

In children with dilated cardiomyopathy, $CoQ_{10}$ may improve the cardiothoracic ratio and shorten ventricular depolarization and NYHA class [122]. In a prospective RCT (duration 6 months) in children with dilated cardiomyopathy, the administration of $CoQ_{10}$ resulted in a lower mean score for the index of cardiac failure ($p < 0.024$ compared to placebo) and in improvement of diastolic function ($p < 0.011$ compared to placebo) [123]. In subjects with hypertrophic cardiomyopathy treated with an average of 200 mg/day of $CoQ_{10}$, a significant improvement in symptoms of fatigue and dyspnoea with no side effects was noted. In addition, the mean interventricular septal thickness (from 1.51 ± 0.17 cm to 1.14 ± 0.13 cm, a 24% reduction, $p < 0.002$) and mean posterior wall thickness improved significantly (from 1.37 ± 0.13 cm to 1.01 ± 0.15 cm, a 26% reduction, $p < 0.005$) [124]. There is also a significant improvement in quality of life (on a 6-min walk test) and NYHA class (≥1) [125].

In the last years, many studies have focused on the role of $CoQ_{10}$ in iatrogenic cardiomiopathies induced by some drugs like anthracycline antibiotics used in the chemotherapy of hematological cancers as leukemias and lymphomas and in solid malignancies such as carcinomas and sarcomas [126]. Doxorubicin is used for the treatment of early-stage breast cancer, and it is known to improve

overall survival. However, side effects such as cardiomyopathy and HF can occur in some patients, probably also for a raised ROS generation. Today, there is data indicating that $CoQ_{10}$ did not have any influence on doxorubicin cell toxicity, thus making further studies urgent [127]. Nevertheless, the administration of $CoQ_{10}$ and L-carnitine in combination showed protection against oxidative stress by reducing levels of malondialdehyde and nitric oxide if started within 5 days before doxorubicin use. In addition, it also improved heart functions and decreased IL-1 and TNF-α Troponin-l and Troponin-T levels [128].

#### 3.2.5. $CoQ_{10}$ and Ischemic Stroke

In the pathophysiology of ischemic stroke, some factors such as inflammation, excitotoxicity, and oxidative stress were demonstrated to play a pivotal role [129,130]. A recent study demonstrated the decrement of $CoQ_{10}$ in the acute phase of ischemic stroke and also the significant negative correlation between serum $CoQ_{10}$ levels and the scores of the NIHSS and MRS (respectively National Institutes of Health Stroke Scale and Modified Ranking Scale) [131]. Ischemia/Reperfusion (I/R) injury may induce oxidative stress and low levels of protective antioxidants such as $CoQ_{10}$ in the brain. In particular, it seems that a decrease of $CoQ_{10}$ induced by I/R overcomes the aging process [132]. In vivo studies (with symptomatic vasospasm model) have reported that pretreatment with $CoQ_{10}$ reduces the incidence of ischemic lesions and can alleviate the pathological outcomes following a stroke incidence [133].

In the last years, the relation between $CoQ_{10}$ and inflammation and oxidative stress has been reported in cell and animal models. Glial fibrillary acidic protein (GFAP), MDA, and superoxide dismutase (SOD) activity are important biomarkers in oxidative stress and neuroinflammatory processes after stroke, and they can predict functional outcomes [134–136]. In a short RCT, 60 patients with acute ischemic stroke were randomly assigned to a placebo or $CoQ_{10}$-supplemented group (300 mg/day) for 4 weeks. At the end of treatment, $CoQ_{10}$ supplementation improved NIHSS and mmSE scores significantly ($p = 0.05$, $p = 0.03$ respectively) even if there were no significant differences in MRS score, SOD, MDA, and GFAP levels between the two groups. These results could be partially explained by the low dose and short duration of supplementation [137].

### *3.3. Special Conditions*

$CoQ_{10}$ supplementation has been tested also in a number of "special conditions", with the aim to evaluate its impact on self-perceived quality of life, instrumental parameters, and sometimes clinical outcomes as well.

#### 3.3.1. Chronic Kidney Disease

Chronic kidney disease (CKD) is associated with an increased prevalence of all-cause mortality, cardiovascular events and hospitalization, and diabetic nephropathy, all regardless of existing risk factors and a history of cardiovascular disease (CVD) [138,139]. Increased biomarkers of oxidative stress in these patients have been identified as a major contributor to the pathogenesis of CKD and related CVD [140,141]. Circulating concentrations of $CoQ_{10}$ have been decreased in patients with CKD, suggesting that $CoQ_{10}$ supplementation may be a potentially useful antioxidant supplement for these patients [142]. Nevertheless, the relation between $CoQ_{10}$ and oxidative stress in patients with CKD is still controversial.

A meta-analysis of seven RCTs demonstrated that $CoQ_{10}$ supplementation to patients with CKD significantly reduced total cholesterol (TC) (SMD = −0.58; CI, −0.94, −0.21; $p = 0.002$), LDL-C (SMD = −0.47; 95% CI, −0.78, −0.17; $p = 0.003$), malondialdehyde (MDA) (SMD = −3.0; 95% CI, −5.10, −0.90; $p = 0.005$), and creatinine levels (SMD = −1.65; 95% CI, −2.75, −0.54; $p = 0.003$) yet did not affect fasting glucose, insulin, HOMA-IR, and C reactive protein (CRP) concentrations [143]. Moreover, in a study not included in the previously cited meta-analysis, $CoQ_{10}$ supplementation at a dosage of 100 mg/day for 12 weeks had positive effects on insulin metabolism and MDA levels among diabetic nephropathy

patients yet fasting glucose remained unchanged [144]. Finally, a recent meta-analysis of 4 RCTs and 4 experimental studies of diabetic people revealed that $CoQ_{10}$ combined with antidiabetic drugs show statistical differences in FPG (SMD = −2.04, 95% CI = −3.90 to −0.18, $p < 0.05$), TC (Std. MD = −1.73, 95% CI = −3.41 to −0.05, $p < 0.05$), HDL-C (Std. MD = 0.09, 95% CI = 0.01–0.18, $p < 0.05$), TG (Std. MD = −0.39, 95% CI = −0.71 to −0.07, $p < 0.05$), and MDA (Std. MD = −1.29, 95% CI = −2.32 to −0.26, $p < 0.05$) amelioration after diabetic kidney disease therapy compared to the control group [145].

$CoQ_{10}$ supplementation for diabetic hemodialysis patients for 12 weeks did not influence lipid profiles [70,146,147]. In hemodialysis patients, 100 mg/day of $CoQ_{10}$ for 3 months could significantly reduce CRP levels (95%CI = −20.1 to −10.5, $p < 0.001$) [148], while daily supplementation with 1200 mg of $CoQ_{10}$ significantly improved biomarkers of oxidative stress [149].

Finally, the supplementation of $CoQ_{10}$ could have a positive impact in people with nephrotic syndrome caused also by a subgroup of mitochondrial diseases classified as primary $CoQ_{10}$ deficiency (pathogenic variants in at least one of 10 genes termed *COQ1* through *COQ10*). In contrast to other mitochondrial disorders, some patients with primary $CoQ_{10}$ deficiency show significant improvements after $CoQ_{10}$ supplementation, making early diagnosis and treatment essential in the management of these people [150].

#### 3.3.2. Migraine

Migraine is an emerging risk factor for both coronary and cerebrovascular diseases [151], for which the pathophysiology has not yet been fully understood. Among other factors, a deficiency of $CoQ_{10}$ is associated with the pathogenesis of migraine, specially in pediatric and adolescent populations [152].

A systematic review and dose-response meta-analysis has been performed evaluating four RCTs including 221 subjects. $CoQ_{10}$ significantly reduced the frequency of migraine attack ($p < 0.001$); however, no significant effect on severity and duration has been observed ($p = 0.105$ and $p = 0.086$, respectively) [153]. A more recent, larger meta-analysis of three RCTs and two observational studies, including 346 patients (120 pediatric and 226 adult subjects), has been carried out. In particular, with a daily dosage of $CoQ_{10}$ of 100 or 400 mg, the forest plot analysis confirmed a significant reduction of the duration of migraine attack/month ($p < 0.00001$) and of the migraine day/month ($p = 0.009$) if compared with placebo. Nevertheless, frequency and severity of attacks ($p = 0.08$) were not changed [154].

Based on this data, the American Academy of Neurology guidelines suggest a possible role of $CoQ_{10}$ in migraine prevention, with a high safety profile in pediatric and adult populations [155].

In one double-blind placebo controlled clinical trial on 45 patients (22 treated with placebo and 23 treated with $CoQ_{10}$ at a dose of 400 mg/day for 3 months), a significant prophilactic effect of the supplementation on migraine attacks was reported, resulting in less severe, shorter, and less frequent attacks. Interestingly, an increase in serum levels of $CoQ_{10}$ and a reduction of TNF$\alpha$ and calcitonin gene-related peptide (GCPR) levels have also been observed, suggesting a role of $CoQ_{10}$ as mitigation of inflammatory processes [156]. According to other studies [43,157], however, no significant differences in serum IL6 and IL10 have been observed compared with the control groups [83].

Interesting results emerge by co-supplementation of $CoQ_{10}$ (100 mg/day) with other nutraceuticals, such as curcumin, magnesium, and *Tanacetum parthenium* L. and riboflavin. In particular, Gaul and collaborators observed on 173 adults affected by migraine that a fixed combination of magnesium (600 mg/day), riboflavin (400 mg/day), and $CoQ_{10}$ (150 mg/day) after 3 months of treatment reduced migraine pain without any serious adverse events [158]. Moreover, preliminary but encouraging results in the prophylaxis of migraine have been observed in a recent RCT, where the assumption of soft gelatin capsules containing nano-micellar curcumin (80 mg/day) and $CoQ_{10}$ (300 mg/day) determined a significant reduction of frequency, severity, and duration of migraine attacks (all $p < 0.001$) [159].

#### 3.3.3. Pre-Eclampsia

Pre-eclampsia is a severe vascular complication of pregnancy. A growing collection of literature suggests that attention needs to be focused on the possible effect of $CoQ_{10}$ during pregnancy-related hypertensive disorders [160].

Pre-eclampsia consists of the gradual development of hypertension, with values of SBP >140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg. However, in some cases, there is worsening of preexisting hypertension, generalized edema, proteinuria (300 mg/L or more in 24 h), and sometimes blood clotting disorders that arise after 20 weeks of gestation [161]. Oxidative stress could be one of the causing factors of this dangerous condition [162]. From one side, pregnant women with established pre-eclampsia have significantly lower plasma levels of $CoQ_{10}$ compared to healthy pregnant women [163,164]. A single trial in which $CoQ_{10}$ has been assumed at the dose of 200 mg/day for 20 weeks until delivery concluded with a reduction of the risk of developing pre-eclampsia in women at risk for the condition ($p = 0.035$) [165]. However, a recent meta-analysis of twenty-nine RCTs highlighted that the antioxidant strategy, both by using of $CoQ_{10}$ and by using of other agents (vitamins, resveratrol, or/and arginine), did not exert significant beneficial effects on maternal and fetal outcomes [166]. Further research is needed in this field.

#### 3.3.4. $CoQ_{10}$ and Statin-Intolerance

Statin-associated myopathy pathogenetic mechanisms are still not fully understood. The most probable hypotheses are related to the increased intracellular lipid production and lipid myopathy, decreased sarcolemmal cholesterol, and reduction in small guanosine triphosphate-binding proteins and in mitochondrial $CoQ_{10}$ [167]. Statins, the milestone in lipid-lowering treatment, inhibit hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate limiting enzyme not only in cholesterol synthesis but also in the synthesis of farnesyl pyrophosphate that is essential for $CoQ_{10}$ biosynthesis, thus explaining the link between statin use and $CoQ_{10}$ deficiency [168]. In fact, a recent meta-analysis of 12 RCTs involving 1776 participants concluded that, compared to the placebo, statin treatment resulted in a reduction of circulating $CoQ_{10}$ (SMD −2.12; 95% CI −3.40 to −0.84; $p = 0.001$) independently from statin solution, intensity, and treatment time [169].

No study has yet been designed to demonstrate that $CoQ_{10}$ supplementation could prevent statin-related myalgia. However, a meta-analysis of 12 RCTs involving 575 patients concluded that, compared to the placebo, $CoQ_{10}$ supplementation ameliorated statin-associated muscle symptoms, such as muscle pain (weighted mean difference (WMD) −1.60; 95% CI −1.75 to −1.44; $p < 0.001$), muscle weakness (WMD −2.28; 95%CI −2.79 to −1.77; $p = 0.006$), muscle cramping (WMD −1.78; 95% CI −2.31 to −1.24; $p < 0.001$), and muscle tiredness (WMD −1.75; 95% CI −2.31 to −1.19; $p < 0.001$), whereas no reduction in plasma creatine kinase levels was observed after $CoQ_{10}$ supplementation (WMD 0.09; 95% CI −0.06 to 0.24; $p = 0.23$) [170]. These positive effects are usually achieved only with high dosages of $CoQ_{10}$ (≥200 mg/day).

However, $CoQ_{10}$ could have a positive impact on the management of patients more likely to develop statin-related side effects. In fact, it has been clinically proven that $CoQ_{10}$ supplementation could be able to improve self-perceived fatigue in healthy subjects, [171] in obese patients [172], and in patients affected by fibromyalgia [173,174] even if larger RCTs are needed to confirm this preliminary data.

## 4. Discussion

Theoretically, $CoQ_{10}$ is an ideal dietary supplement. It is contained in some foods, its dosage in blood is feasible, and its deficiency is associated with some diseases, while its supplementation tends to restore a physiological condition (Table 2). Moreover, the supplementation with $CoQ_{10}$ is safe, even with chronic exposure to 900 mg/day [175] and in frail patients, like elderly and CKD patients, without any known pharmacological interactions [3].

**Table 2.** Coenzyme $Q_{10}$: clinical applications in cardiovascular diseases.

| | Level of Evidence | Active Daily Doses | Effects on Symptoms and/or Grade of Disease | Effects on Lab or Instrumental Parameters | Effects on Hard Outcomes |
|---|---|---|---|---|---|
| **Heart Failure (HF)** | Meta-analysis of RCTs | 100–300 mg | ↑ self-perceived quality of life and improvement in NYHA class | ↑ EF (if >30%), ↑ LVEF, ↑ CO and CI, ↑ SV, ↑ EDV, ↑ exercise capacity, ↓ ventricular arrhythmias after surgery and need of inotropic drugs (after cardiac surgery), and ↓ low-grade inflammation (TNF-alpha, IL-6, and hsCRP) | ↓ MACE, total mortality, and incidence of hospital stays for HF |
| **Acute Myocardial Infarction (AMI)** | RCTs | 120 mg | Not investigated | Prevention of alteration of the wall thickening abnormality at the infarct site and sphericity index and ↓ wall thickness opposite the site of infarction | Not investigated |
| **Ischemic Stroke (IS)** | RCTs | 300 mg | ↑ NIHSS and mmSE | Reduction of oxidative stress (?) | Not investigated |
| **Atrial Fibrillation (AF)** | Meta-analysis of RCTs | 100–300 mg | Improvement in NYHA class, reduction of risk to develop ventricular arrhythmias, and use of inotropic drugs after surgery | Reduction of malondialdehyde and oxidative stress | Not investigated |
| **Cardiomyopathy** | RCTs | 200–300 mg | Improvement of fatigue and dyspnea | Improvement of mean interventricular septal thickness, mean posterior wall thickness, diastolic function, and mean score for the index of cardiac failure | Not investigated |
| **Cardiotoxicity** | RCTs | 200–300 mg | Improvement of heart's functions (in association with L-carnitine) | Reduction of oxidative stress (nitric oxide and malondialdehyde) and ↓IL-1, TNF-α Troponin-l and Troponin-T levels (in association with L-carnitine) | Not investigated |
| **Hypertension** | Meta-analysis of RCTs | 100–300 mg | Not reported | ↑ Exercise capacity and arterial stiffness, ↑ NO bioavailability, and ↓ SBP and DBP (only in prehypertensive or hypertensive patients) | Not investigated |
| **Diabetes type II, Metabolic syndrome (MetS)** | RCTs | 100–300 mg | Not reported | ↓ Lipid peroxidation, FPG, triglycerides, and low-grade inflammation (TNF-alpha, IL-6, and hsCRP) and ↑ insulin sensitivity | Not investigated |
| **Dyslipidemia** | RCTs | 100–300 mg | ↑ self-perceived quality of life (reduction side effects of lipid-lowering drugs) | ↑ Exercise capacity and arterial stiffness; ↓ lipid peroxidation, TC*, LDL-C*, TG*, BP*, FPG*, and low-grade inflammation (TNF-alpha, IL-6, and hsCRP); and ↑ insulin sensitivity<br>*If >12 weeks of treatment | Not investigated |
| **Non-Alcoholic Fatty Liver Disease (NAFLD)** | Meta-analysis of RCTs | 100–300 mg | Improvement in NAFLD grade | ↑ Adiponectin (?) and leptin levels; ↓ AST, GGT, hsCRP, and TNF-alpha levels; and ↓ WC and lipid peroxidation | Not investigated |
| **Chronic Kidney Disease (CKD)** | Meta-analysis of RCTs | 100–300 mg | Not investigated | ↓ Lipid peroxidation, TC (?), LDL-C (?), Lp(a) (?), triglycerides (?), fasting plasma glucose (?), HbA1c (?), inflammation, and oxidative stress biomarkers (hsCRP (?) and malondialdehyde) and ↑ insulin sensitivity | Not investigated |

AST = Aspartate Aminotransferase, BP = Blood Pressure, CI = Cardiac Input, CO = Cardiac Output, DBP = Diastolic Blood Pressure, EDV = End-Diastolic Volume, EF = Ejection Fraction, FPG = Fasting Plasma Glucose, GGT = Gamma-Glutamyl Transpeptidase, HF = Heart Failure, hsCRP = high sensible C-Reactive Protein, IL-6 = Interleukin 6, LDL-C = LDL-Cholesterol, Lp(a) = Lipoprotein a, LVEF = Left Ventricular Ejection Fraction, MACE = Major Adverse Cardiac Events, mmSE = Mini Mental State Examination, NIHSS = National Institute of Health Stroke Scale, NYHA = New York Heart Association, NO = Nitric Oxide, RCTs = Randomized Clinical Trials, SBP = Systolic Blood Pressure, SV = Stroke Volume, TC = Total Cholesterol, TG = triglycerides, TNF-alpha = Tumor Necrosis Factor-alpha, WC = Waist Circumference. ↓: Worsening; ↑: Improvement; ?: Unclear.

The results derived from clinical trials testing the efficacy of $CoQ_{10}$ supplementation in different settings are often contrasting and complicate the process of making definitive conclusion on its efficacy in a number of conditions. This is due to a series of causes: the studies are often underpowered, the duration is too short to test the effects on hard outcomes, the methodology applied is sometime of low quality with a scarce standardization of patients characteristics at the baseline, the tested dosage is not titrated based on the blood $CoQ_{10}$ level, and there is usually no quantification of $CoQ_{10}$ intake with diet (even if this is usually very low). However, one of the most important problems about $CoQ_{10}$ is related to its poor oral bioavailability. In fact, most of the $CoQ_{10}$ integrated is eliminated through the faeces and only a fraction of that supplement reaches the blood and thus the tissues and organs [176]. $CoQ_{10}$ is a molecule with relatively high molecular weight (MW = 863) and is insoluble in water. Because of these reasons, it is poorly absorbed in the gastrointestinal tract, and the key to effective supplementation is therefore the improvement of its bioavailability [177]. Intestinal absorption of $CoQ_{10}$ occurs firstly through the emulsification and formation of "mixed micelles" with fatty meal constituents, also facilitated by bile and pancreatic secretions in the small intestine. It is therefore important to stress that the assumption of $CoQ_{10}$ in fed state can significantly improve its absorption [178]. The absorption efficiency is well known to be dose dependent and occurs through a "simple passive facilitated diffusion" process: "passive" because it does not require the use of energy and "facilitated" because the intestinal transport is made possible by a lipid carrier, which is usually a monoglyceride fat [179]. In the enterocytes, $CoQ_{10}$ is incorporated into chylomicrons and subsequently reaches the bloodstream through the lymphatic system (Figure 3). The results of pharmacokinetic studies conducted using deuterium-labeled $CoQ_{10}$ [180] demonstrated slow absorption in the gastrointestinal tract ($T_{max} \approx 6$ h) with a second plasma peak observed approximately 24 h after the oral intake [179]. This second peak could be attributed to both enterohepatic recirculation and hepatic redistribution of the circulation, mainly through the LDL/VLDL fractions [178].

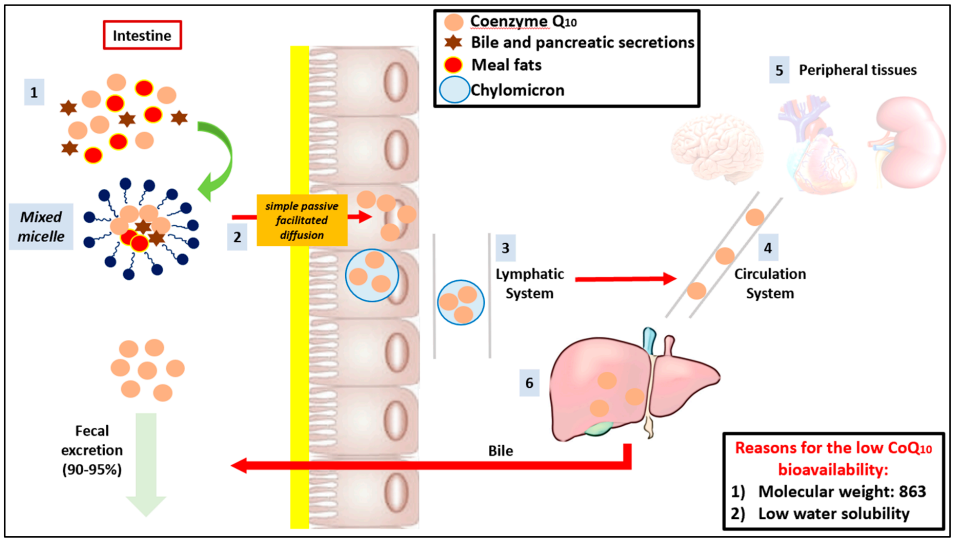


**Figure 3.** Coenzyme $Q_{10}$ physiology: (1) $CoQ_{10}$ arrives in intestinal lumen with exogenus cholesterol after a meal (if administered in fed state. (2) $CoQ_{10}$ is taken up from the mixed micelles, together with the meal fats and bile and pancreatic secretions, which facilitate its solubilization and the entrance in the enterocytes via the simple passive facilitated diffusion. (3) $CoQ_{10}$ is incorporated in the chylomicrons and subsequently reaches the bloodstream through the lymphatic system. (4) Through the bloodstream, $CoQ_{10}$ is distributed to peripheral tissues (5) and to the liver (6), where it is partially re-excreted in the bile and eliminated with the faeces.

To date, various formulations and dosages of $CoQ_{10}$ are present on the market, such as tablets, chewable tablets, capsules, and gels containing oily suspensions. However, the oral bioavailability of this supplement is extremely variable in relation to many aspects. For example, the type of formulation and the release method, the dosage of $CoQ_{10}$, and the mode of administration (e.g., with or without water

and before or after meals) are biopharmaceutical factors that may affect bioavailability, as highlighted before [181]. Regarding the molecule, the ubiquinol form is the most available compared to ubiquinone, in particular if supplemented in fed state and conveyed through specific strategies like the use of liposomes, nano-emulsions nanostructured lipid carriers, and micelles [182,183]. The reduction of particle size (including the use of nanoparticles), the use of oily suspensions, and the solubilization and increase of solubility in water are also viable strategies [184]. In particular, the $CoQ_{10}$ and β-cyclodextrin complex has been developed in addition to the intention of improving solubility in water to implement the technological properties and stability of $CoQ_{10}$ [185], permitting the preparation of aqueous formulations, such as syrups. The improvement of bioavailability with $CoQ_{10}$ + β-cyclodextrins and with ubiquinol have already been demonstrated in humans [186–188], with satisfactory results. Table 3 summarizes the main biopharmaceutical strategies used to increase the bioavailability of $CoQ_{10}$.

**Table 3.** Comparative study of $\Delta C_{max}$ after a single dose of different formulations of $CoQ_{10}$ (adapted from López-Lluch et al. [188]).

| Type of Formulation | Subjects | Tested Dosage | ΔCmax | Reference |
|---|---|---|---|---|
| Myoquinon (softgel) | Both gender (10 M, 4 F), age 18–30 | 100 mg | 1.069 | [189] |
| KOJ, $CoQ_{10}$ (softgel) | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.238 | |
| ICT, $CoQ_{10}$ (softgel) | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.351 | |
| ERG, $CoQ_{10}$ (softgel) | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.258 | |
| Ubquinol QH (softgel) | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.473 | |
| NYD $CoQ_{10}$ (hard gel) | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.381 | |
| SMF $CoQ_{10}$ | Both gender (10 M, 4 F), age 18–30 | 100 mg | 0.181 | |
| Capsule $CoQ_{10}$ | 9 M, age 18–30 | 30 mg | 0.31 | [190] |
| Gelatin capsule $CoQ_{10}$ + vitamin E | Both gender (12 M, 12 F) | 100 mg | 0.025 | [191] |
| NanoSolve (purified phospholipids) capsule $CoQ_{10}$ + vitamin E | Both gender (12 M, 12 F) | 100 mg | 0.103 | |
| Capsule $CoQ_{10}$ (powder-filled hard-shell gelatine capsule) | Both gender (3 M, 3 F), age 18–40 | 250 mg | 0.490 | [192] |
| Liquid (O/W liquid emulsion (20 mg/mL)) | Both gender (3 M, 3 F), age 18–40 | 250 mg | 0.980 | |
| Chewable wafer | Both gender (15 M, 10 F), elderly people | 600 mg | 0.770 | [193] |
| Chewable wafer + 300 IU vitamin E | Both gender (15 M, 10 F), elderly people | 600 mg | 0.660 | |
| Softgel capsules (Mega Q-Gel "100") $CoQ_{10}$ solubilized in an oil-based vehicle + 900 IU d-alpha tocopherol | Both gender (15 M, 10 F), elderly people | 600 mg | 0.690 | |
| Hard gelatin capsule | Both gender (15 M, 10 F), elderly people | 600 mg | 0.660 | |
| Powder | | 333 mg | 0.980 | [194] |
| Kaneka QH, ubiquinol (softgel capsules) | Both gender (5 M, 5 F) | 150 mg | 1.061 | [195] |
| | 5 M | 300 mg | 2.506 | |
| Chewable tablets | 10 M, age 21–28 | 150 mg | 0.120 | [196] |
| Capsule liquid | 10 M, age 21–28 | 150 mg | 0.149 | |
| Capsule liquid | 10 M, age 21–28 | 150 mg | 0.152 | |
| Capsule powder | 10 M, age 21–28 | 150 mg | 0.175 | |
| Capsule liquid | 10 M, age 21–28 | 150 mg | 0.197 | |
| Softgel | 10 M, age 21–28 | 150 mg | 0.277 | |
| Q-gel ($CoQ_{10}$ solubilized in an oil-based vehicle + vitamin E) softgel | 10 M, age 21–28 | 150 mg | 0.506 | |
| Q-gel ($CoQ_{10}$ solubilized in an oil-based vehicle + vitamin E) softgel | 8 M, age 20–26 | 60 mg<br>150 mg<br>300 mg | 0.267<br>0.802<br>1.010 | |
| Softgel $CoQ_{10}$ | 36 M, age 18–40 | 100 mg | 0.259 | [197] |
| Softgel $CoQ_{10}$ + sterols | 36 M, age 18–40 | 100 mg | 0.189 | |
| Hardgel ($CoQ_{10}$ + 400 mg 400 mg of Emcompress) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 0.775 | [180] |
| Softgel Bioqinon ($CoQ_{10}$ + 400 mg of soybean oil) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 1.454 | |
| Softgel ($CoQ_{10}$ + 20 mg of polysorbate 80, 100 mg of lecithin + 280 mg of soybean oil) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 0.837 | |
| Softgel ($CoQ_{10}$ + 20 mg of polysorbate 80 + 380 mg of soybean oil) | Both gender (5 M, 5 F), age 24–30 | 100 mg | 0.883 | |

Myoqinon (soy-oil matrix, drug specification heat/cooling recrystallization procedure); KOJ, $CoQ_{10}$ (same as Myoqinon but without heat/cooling procedure); ICT, $CoQ_{10}$ (olive oil, cocoa-butter produced accordingly normal softgel filling technology); ERG, $CoQ_{10}$ (olive oil, cocoa-butter, 25 mg vitamin C produced accordingly normal softgel filling technology); Ubiqinol QH (MCT-oil, 12 mg vitamin C); NYD, $CoQ_{10}$ (fine grinded (micronized) $CoQ_{10}$ powder); SMF, $CoQ_{10}$ (olive-oil/soy-oil matrix produced accordingly normal softgel filling technology); NanoSolve (Lipoid GmbH, Ludwigshafen, Germany); Kaneka QH (ubiquinol emulsified with diglycerol monooleate, rapeseed oil, soy lecithin, and beeswax).

Even though these formulations allow an important increase of bioavailability, it is important to underline that most of the orally supplemented $CoQ_{10}$ is eliminated via faeces [175]. Furthermore, $CoQ_{10}$ exerts many mild positive effects on different tissues and metabolism. They could individually not be so relevant from a quantitative point of view, but it is really difficult to quantify their impact as a whole on human health. In fact, the long-term contemporary reduction of systemic inflammation and oxidative stress, a mild reduction of blood pressure, and insulin-resistance could have positive impacts on cardiovascular disease risk.

## 5. Conclusions

Clinical evidence supports supplementation with high doses of bioavailable-$CoQ_{10}$ (≥200 mg/day) to support heart health in patients affected by coronary heart disease and heart failure, partly modulating a number of risk factors for these conditions, and partly directly acting on myocardial cell metabolism. Long-term RCTs are still needed to confirm and better understand the efficacy and safety profile of this molecule in a large number of patients and CV diseases.

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