Nutritional Intervention of Coenzyme Q10 in Energy Metabolism, Cardiovascular Health, Neurological Function, and Anti-Aging

Mechanistic Pathways and Clinical Evidence within the Three-Axis, Seven-Module Framework

Abstract

Coenzyme Q10 (Co-Q10), a lipid-soluble quinone cofactor participating in both mitochondrial bioenergetics and antioxidant defense, represents one of the most extensively characterized bioactive nutrients in clinical nutrition science.

Within *the Three-Axis, Seven-Module Framework* proposed by Keyora, Co-Q10's functions are systematically reinterpreted as a multi-dimensional network integrating energy metabolism, redox regulation, cardiovascular protection, neuroprotection, and anti-aging.

Axis I – Mitochondrial Energy Axis: delineates Co-Q10 as the central electron carrier between Complexes I/II and III in the electron transport chain, sustaining ATP synthesis and maintaining the proton motive force.

Human RCTs (e.g., Q-SYMBIO, KISEL-10) confirm its ability to enhance myocardial contractility, improve exercise tolerance, and reduce cardiovascular events.

In athletes and chronic fatigue patients, supplementation (100-300 mg/day) increases

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VO_2max, accelerates lactate clearance, and alleviates fatigue, while aging cohorts demonstrate improved vitality and reduced functional decline through restored mitochondrial efficiency.

Axis II – Antioxidant and Cellular Protection Axis: emphasizes Co-Q10's redox cycling (ubiquinone ↔ ubiquinol) as the basis for sustained free radical scavenging and regeneration of vitamin E/C.

This antioxidant loop mitigates oxidative injury, preserves endothelial function, and prevents inflammatory remodeling, thereby supporting cardiovascular and cellular homeostasis.

Synergistic interactions with selenium and other micronutrients (as evidenced in the KISEL-10 study) amplify both antioxidant and cardio-protective effects.

Axis III – Disease Intervention and Anti-Aging Axis: extends Co-Q10's implications to pathological and aesthetic medicine.

In neurological disorders (Parkinson's, Alzheimer's, migraine), Co-Q10 preserves neuronal mitochondria and dopaminergic integrity.

In statin-associated myopathy, it replenishes depleted stores, mitigating muscle symptoms.

In dermatological and anti-aging contexts, oral (100–200 mg/day) and topical Co-Q10 enhance dermal ATP supply, reduce MMP-mediated collagen degradation, and improve elasticity, hydration, and wrinkle parameters in controlled clinical trials.

Collectively, the evidence positions Co-Q10 as a dual-function molecular hub bridging energy production and redox equilibrium. Across cardiovascular, neurological, muscular, and dermatological systems, it exhibits robust translational efficacy, excellent safety, and long-term tolerability.

The *Three-Axis, Seven-Module Framework* provides a unifying model for understanding its systemic bioactivity, clinical applicability, and integration into preventive, therapeutic, and anti-aging strategies.

Keywords

Coenzyme Q10 (Co-Q10); ubiquinone; ubiquinol; mitochondrial energy metabolism; electron transport chain; ATP synthesis; oxidative phosphorylation; antioxidant defense; reactive oxygen species (ROS); proton motive force (PMF); cardiovascular protection; heart failure; coronary artery disease; angina pectoris; endothelial function; inflammation; neuroprotection; Parkinson’s disease; Alzheimer’s disease; statin-associated muscle symptoms (SAMS); fatigue; exercise performance; VO_2max; chronic fatigue syndrome (CFS); aging; mitochondrial dysfunction; oxidative stress; skin aging; collagen synthesis; dermal elasticity; KISEL-10 trial; Q-SYMBIO trial; selenium synergy; nutritional intervention; clinical nutrition; anti-aging medicine; bioenergetic regulation; functional supplementation; preventive health.

Overview of Coenzyme Q10 (Coenzyme Q10, Co-Q10)

Coenzyme Q10, also known as ubiquinone, is a lipid-soluble quinone compound widely distributed in the mitochondrial membranes of human cells. Its structure consists of a benzoquinone ring with ten isoprenoid side chains (hence the designation Q10), and it functions both as an electron carrier and as an antioxidant. In the human body, Coenzyme Q10 exists in two interconvertible forms:

- Oxidized form (ubiquinone): Transfers electrons in the mitochondrial electron transport chain (ETC), driving ATP synthesis.
- Reduced form (ubiquinol): Acts as a potent lipid-soluble antioxidant, scavenging free radicals, preventing lipid peroxidation, and regenerating other antioxidants such as vitamin E and vitamin C.

These two forms are in constant dynamic equilibrium:

- In the ETC, the oxidized form is reduced to ubiquinol after receiving electrons.
- During free radical scavenging, ubiquinol donates electrons and is oxidized back to ubiquinone.

This continuous redox cycling enables Coenzyme Q10 to sustain both mitochondrial energy metabolism and antioxidant defense simultaneously. Thus, Coenzyme Q10 functions as a unique dual-role molecular hub, integrating bio-energetic supply with cellular protection.

Biosynthesis and Metabolism

Coenzyme Q10 is primarily synthesized endogenously, via a pathway shared with cholesterol biosynthesis, dependent on the enzyme HMG-CoA reductase. Consequently, pharmacological inhibition of this enzyme (e.g., by statins) significantly reduces Coenzyme Q10 synthesis.

Although Coenzyme Q10 can also be obtained from dietary sources (such as animal heart tissue, fish, and nuts), exogenous intake is generally insufficient to reach clinically effective dosages.

Physiological Functions

Coenzyme Q10 fulfills two central physiological roles:

- Core factor of energy metabolism: Functions as an electron carrier between complex I/II and complex III of the ETC, indispensable for ATP production.
- Lipid-soluble antioxidant: Neutralizes free radicals within cellular membranes and lipid environments, prevents lipid peroxidation, and regenerates antioxidant vitamins (E and C).

Because of its dynamic ubiquinone ↔ ubiquinol conversion, Coenzyme Q10 exerts dual and complementary roles:

- Bio-energetic function: Maintains ATP synthesis in energy-demanding tissues such as the heart, skeletal muscle, and neurons.
- Antioxidant protection: Defends against lipid peroxidation, DNA oxidation, and protein damage.

Clinical Significance

Coenzyme Q10 demonstrates broad clinical value across multiple domains:

- Cardiovascular health: Improves myocardial bioenergetics and endothelial function in patients with heart failure, coronary artery disease, and hypertension.
- Neurological support: Provides neuroprotection and cognitive benefits in Parkinson’s disease, Alzheimer’s disease, and migraine.
- Exercise performance and fatigue recovery: Enhances endurance capacity and accelerates post-exercise recovery.
- Drug-related deficiency: Mitigates statin-associated muscle symptoms (SAMS) by replenishing depleted Coenzyme Q10.
- Skin health and anti-aging: Reduces photoaging damage, stimulates collagen synthesis, and supports skin repair and rejuvenation.

A Systematic Interpretation of the Multi-Dimensional Interventions of Coenzyme Q10

Discussion and Evidence within the "Three-Axis, Seven-Module Framework"

Coenzyme Q10, as a nutritional molecule with a dual identity - both a core factor in energy metabolism and a lipid-soluble antioxidant - exerts biological effects that go far beyond single-mechanism explanations.

Earlier research largely focused on its isolated applications in cardiovascular or neurological diseases. However, with deeper insights into the interplay among mitochondrial function, oxidative stress, and cellular metabolism, it has become increasingly clear that the role of Coenzyme Q10 should be understood within a multi-dimensional, cross-system framework.

Following this perspective, Keyora has proposed the *Three-Axis, Seven-Module Framework,* which systematically summarizes and delineates the core efficacy and clinical value of Coenzyme Q10.

This framework categorizes the physiological and clinical roles of Coenzyme Q10 into three primary dietary-nutritional intervention axes and seven functional modules:

1) Axis I – Mitochondrial Energy Axis

Highlights the pivotal role of Coenzyme Q10 in ATP generation and exercise energy metabolism.

2) Axis II – Antioxidant and Cellular Protection Axis

Focuses on its value in free radical scavenging, defense against lipid peroxidation, and cardiovascular protection.

3) Axis III – Disease Intervention and Anti-Aging Axis

Explores its applications in neurodegenerative disorders, drug-induced deficiencies, and skin anti-aging.

Under these three axes, seven functional modules are delineated, mapping a complete landscape of Coenzyme Q10's mechanisms and actions.

This model not only clarifies the mechanistic pathways of Coenzyme Q10 but also provides a theoretical foundation for precise positioning and targeted intervention strategies across different clinical populations.

The following discussion will begin with *Axis I – Mitochondrial Energy Axis*, starting from *Module I – ATP Generation and Cellular Energy Metabolism*, to examine in depth the central role of Coenzyme Q10 in cellular bioenergetics.

Axis I – Mitochondrial Energy Axis

Among all the biological functions associated with Coenzyme Q10, mitochondrial energy metabolism stands as the most fundamental and central.
As the “powerhouse” of ATP synthesis, mitochondria rely on the efficient operation of the electron transport chain (ETC) to meet the high energy demands of organs such as the heart, skeletal muscle, and the nervous system.

Coenzyme Q10 is an indispensable electron carrier in this process, situated between Complex I/II and Complex III, and determining whether electron flux can proceed smoothly to drive ATP synthesis.

Importantly, Coenzyme Q10 functions not only as a “conduit” for electron transport but also as a regulatory hub of bioenergetics. When Coenzyme Q10 levels decline, ATP synthesis efficiency rapidly deteriorates, leading to impaired myocardial contractility, reduced exercise tolerance, and systemic metabolic disturbances.
Conversely, sufficient Coenzyme Q10 availability significantly enhances cellular energy supply and improves the body’s adaptability to high-energy demands.

Therefore, within the *Keyora Three-Axis, Seven-Module Framework*, the Mitochondrial Energy Axis is prioritized as the first discussion point. It establishes the physiological foundation of Coenzyme Q10 as an “energy molecule” and provides the logical starting point for understanding its multi-dimensional functions in antioxidant defense, cardiovascular protection, and neurological support.

I Module I – ATP Generation and Cellular Energy Metabolism

Within the *Three-Axis, Seven-Module Framework*, ATP generation and cellular energy metabolism are positioned as the first functional module. This prioritization reflects not only the core biological role of Coenzyme Q10 but also its foundational relevance to all subsequent mechanisms of action.

Mitochondria are often described as the “cellular power plants,” with ATP serving as the immediate energy currency of all life processes. The efficiency of ATP synthesis depends on the proper functioning of the ETC, where Coenzyme Q10 occupies the critical bottleneck position.

As the electron carrier between Complex I/II and Complex III, Coenzyme Q10 ensures the continuity of electron transport and efficient coupling to ATP production. Any reduction in Coenzyme Q10 availability disrupts this flow, resulting in decreased ATP output and abnormal accumulation of reactive oxygen species (ROS).

This mechanism explains why energy-intensive tissues such as the heart, skeletal muscle, and neurons are particularly dependent on Coenzyme Q10, and why its deficiency leads to characteristic clinical manifestations.

The central objective of Module I is therefore to systematically delineate the indispensable role of Coenzyme Q10 in ATP synthesis - integrating molecular mechanisms, experimental evidence, and clinical studies.

This establishes its unique therapeutic value in conditions such as cardiovascular disease, fatigue syndromes, and age-related energy impairments.

1) Mechanistic Basis

1.1) Coenzyme Q10 as a Central Hub in the Electron Transport Chain (Detailed Elaboration)

Coenzyme Q10 (Coenzyme Q10, Co-Q10), in its oxidized form (ubiquinone), is embedded within the hydrophobic region of the inner mitochondrial membrane, where its high mobility allows it to diffuse freely through the lipid bilayer.

This unique distribution enables Co-Q10 to serve as the key electron acceptor from both Complex I (NADH dehydrogenase) and Complex II (succinate dehydrogenase).

- Complex I pathway: Electrons derived from NADH, generated during glycolysis and the tricarboxylic acid (TCA) cycle, are transferred to Complex I. From there, they are passed to oxidized Co-Q10, which is reduced to ubiquinol.

- Complex II pathway: Succinate is oxidized to fumarate via Complex II, and the resulting electrons are transferred through $FADH_2$ to oxidized Co-Q10, similarly reducing it to ubiquinol.

At these two converging entry points, virtually all reducing equivalents are funneled into Co-Q10, making it the collection node of cellular energy metabolism. The reduced form then transfers electrons to Complex III (cytochrome bc1 complex), continuing the chain of electron flow toward cytochrome c.

This process is tightly coupled to the function of proton pumps:

- During electron transfer through Complexes I and III, protons (H^+) are pumped across the inner mitochondrial membrane into the intermembrane space.
- This establishes a transmembrane proton gradient, or proton motive force (PMF), which provides the potential energy required to drive ATP synthase.

Thus, Co-Q10 is far more than a passive “electron conduit”; it acts as a bio-energetic hub in mitochondrial energy conversion:

- Without Co-Q10, electron flux would stall at Complex I/II, and proton pumping would fail to proceed.

- As a consequence, ATP synthesis would sharply decline, while electron leakage would increase, leading to excessive accumulation of reactive oxygen species (ROS).

From a systems perspective, this mechanism renders Co-Q10 indispensable for sustaining the function of energy-demanding organs such as the heart, skeletal muscle, and nervous system. Its intracellular levels correlate almost linearly with ATP production rates. This explains why Co-Q10 deficiency most prominently manifests as cardiac dysfunction, skeletal muscle fatigue, and neuronal impairment.

1.2) Proton Gradient Formation and ATP Synthesis (Detailed Elaboration)

In the operation of the electron transport chain (ETC), Coenzyme Q10 functions not only as an electron carrier but also as an indirect driver of the proton motive force (PMF) that underpins oxidative phosphorylation.

A. Coupling of Transmembrane Proton Translocation

- When ubiquinol donates electrons to Complex III (cytochrome bc1 complex), the process known as the Q-cycle is initiated.
- During this cycle, ubiquinol is oxidized back to ubiquinone, while its released electrons follow two separate routes: one is transferred to cytochrome c, and the other recycles back to the Co-Q10 binding site.

- This dual-channel electron flow drives Complex III to pump multiple protons (H^+) from the mitochondrial matrix into the intermembrane space.

B. Establishment of the Proton Electrochemical Gradient

- Through the continuous operation of Complexes I, III, and IV, a marked proton concentration gradient and membrane potential difference are established across the inner mitochondrial membrane.
- This transmembrane electrochemical gradient, known as the proton motive force, serves as the immediate energy reservoir for cellular energy conversion.

C. Driving Mechanism of ATP Synthase

- Complex V (ATP synthase), embedded in the inner membrane, utilizes its F_o subunit to form a proton channel.
- As protons flow back into the matrix along their gradient, they induce conformational changes in the F_1 catalytic subunit, enabling the phosphorylation of ADP to ATP (ADP + Pi $\rightarrow$ ATP).
- It is estimated that the oxidation of one molecule of NADH ultimately yields approximately 2.5 molecules of ATP through this process, with Co-Q10 cycling continuously between its reduced and oxidized states at each step.

D. Determinants of Bio-energetic Efficiency

- The efficiency of electron transfer between Complex I/II and Complex III, mediated by Co-Q10, directly determines proton pump activity and the stability of the PMF.
- When Co-Q10 availability declines, electron transport becomes impaired, proton pumping efficiency falls, PMF weakens, and ATP synthesis diminishes sharply.
- Under these conditions, excess electrons readily "leak" to oxygen, generating superoxide anions (O_2^{-}•) and exacerbating oxidative stress.

Summary:

Coenzyme Q10 serves as the central switch for proton gradient formation and ATP synthesis. It not only ensures continuity of electron flow but also fuels proton pumping, thereby enabling mitochondria to efficiently convert substrate oxidation energy into ATP. This mechanism forms the indispensable basis for the proper functioning of high-energy organs such as the heart, skeletal muscle, and the nervous system.

1.3) Dynamic Redox Cycling

The uniqueness of Coenzyme Q10 lies in its continuous cycling between the oxidized form (ubiquinone) and the reduced form (ubiquinol). This property enables it to simultaneously function as both a bio-energetic hub and an antioxidant defense factor.

A. Redox Cycling in Electron Transport

- When Complex I/II transfers electrons to Coenzyme Q10, oxidized ubiquinone accepts the electrons and is reduced to ubiquinol.
- Subsequently, in the Q-cycle of Complex III (cytochrome bc1 complex), ubiquinol donates its electrons and reverts back to the oxidized form.
- This alternating redox transformation ensures the continuity of electron flow and the proper operation of proton pumps.

B. Redox Cycling in Antioxidant Defense

- During free radical scavenging, reduced ubiquinol serves as an electron donor to neutralize reactive oxygen species (ROS), becoming oxidized in the process.
- Oxidized ubiquinone can then be reduced back to ubiquinol by the mitochondrial respiratory chain or by intracellular enzyme systems, thus completing a sustained antioxidant cycle.
- This recurring mechanism allows Coenzyme Q10 to exert long-term free radical scavenging activity within membranes and lipid-rich environments.

C. Dual Functional Significance

- Bio-energetic perspective: This cycling is essential for the efficient operation of the ETC and determines the rate of ATP synthesis.

- Antioxidant perspective: It enables Coenzyme Q10 to repeatedly neutralize ROS while regenerating other antioxidants such as vitamin E and vitamin C, thereby contributing to a synergistic cellular defense network.

Summary:

Through its dynamic transformation between ubiquinone ↔ ubiquinol, Coenzyme Q10 occupies a unique position as a dual hub of energy and antioxidant defense.

This mechanism ensures not only the continuity of cellular energy metabolism but also provides persistent oxidative protection for the organism.

1.4) Dependency of High-Energy Tissues

Although Coenzyme Q10 is distributed throughout all human tissues, its importance is particularly pronounced in high-energy organs such as the heart, skeletal muscle, and nervous system. These tissues require a constant and abundant supply of ATP to sustain contraction, conduction, and metabolic activity. Because of their reliance on mitochondrial oxidative phosphorylation, they are especially dependent on Coenzyme Q10 as a key molecular driver.

A. Cardiac Tissue

- Cardiomyocytes are among the most mitochondria-rich cells in the human body, with mitochondria occupying more than 30% of their volume.

- The contractile pumping function of the heart relies almost entirely on continuous ATP supply from mitochondria.
- When Coenzyme Q10 levels decline, the efficiency of the ubiquinone ↔ ubiquinol cycle is impaired, electron transport stalls, and myocardial contractility diminishes.
- Clinical studies have demonstrated that patients with heart failure exhibit significantly lower myocardial Coenzyme Q10 concentrations compared to healthy controls; supplementation improves ejection fraction and exercise capacity.

B. Skeletal Muscle

- Skeletal muscle energy consumption rises dramatically during physical activity, requiring rapid mitochondrial ATP production.
- In the absence of sufficient Coenzyme Q10, electron transport efficiency falls, ATP synthesis becomes inadequate, and exercise tolerance is reduced, leading to premature fatigue.
- Interventional trials in athletes and physically active individuals have shown that Coenzyme Q10 supplementation shortens post-exercise recovery time, suggesting enhanced efficiency of energy turnover.

C. Nervous System

- Neurons are highly energy-demanding cells; synaptic activity and neurotransmitter release depend on uninterrupted ATP availability.

- Coenzyme Q10 deficiency leads to reduced neuronal ATP, impaired maintenance of membrane potential, and increased ROS accumulation, all of which can trigger neuronal apoptosis.
- In patients with Parkinson's disease and Alzheimer's disease, mitochondrial dysfunction has been closely associated with reduced Coenzyme Q10 levels; supplementation has been reported to improve certain neurological functional parameters.

Summary:

In high-energy tissues, Coenzyme Q10 sustains the continuity of the electron transport chain and the efficiency of ATP synthesis through its dynamic ubiquinone ↔ ubiquinol redox cycling. Deficiency results not only in energy insufficiency but also in accelerated tissue damage due to ROS accumulation.

This dual mechanism fundamentally explains the clinical value of Coenzyme Q10 in cardiovascular disease, exercise-induced fatigue, and neurodegenerative disorders.

2) Clinical Evidence and Consensus

2.1) Heart Failure

A. Clinical Trial Evidence – The Q-SYMBIO Study

The Q-SYMBIO trial (2014) remains the landmark investigation evaluating Coenzyme Q10 in heart failure. This international, multicenter, randomized, double-blind, placebo-controlled study enrolled 420 patients with moderate to severe chronic heart failure (NYHA class II–III, LVEF ≤ 35%).

- Intervention: Patients were randomized to receive either oral Coenzyme Q10 300 mg/day (divided into three doses) or placebo.
- Follow-up duration: 2 years.
- Primary endpoints: Cardiovascular mortality, heart failure–related hospitalization, and clinical deterioration.
- Secondary endpoints: Left ventricular ejection fraction (LVEF) and improvement in NYHA functional class.

B. **Key Findings**

- Over the 2-year follow-up, the incidence of major adverse cardiac events (MACE) was significantly lower in the Coenzyme Q10 group (15% vs. 26%, $p < 0.01$).
- Cardiovascular mortality was reduced by approximately half (9% vs. 16%).
- Heart failure–related hospitalizations declined, indicating improved disease stability.
- LVEF improved by an average of >6% in the intervention group, with more patients showing functional recovery from NYHA class III to II or I.

- Coenzyme Q10 was well tolerated, with no serious treatment-related adverse effects reported.

This trial provided the first large-scale, long-term RCT evidence demonstrating that Coenzyme Q10 supplementation improves prognosis in chronic heart failure—not only by enhancing myocardial ATP generation and contractile performance but also by stabilizing cardiomyocytes through antioxidant mechanisms, thereby reducing mortality and hospitalization rates.

C. Clinical Consensus

Building on Q-SYMBIO and subsequent RCTs and systematic reviews, an international consensus has gradually emerged:

- Evidence base: Coenzyme Q10 is considered one of the few nutritional adjuncts for heart failure supported by robust long-term RCT evidence.
- Mechanistic rationale: Improves cardiac function through multiple pathways—by enhancing mitochondrial bioenergetics, boosting contractile efficiency, and attenuating oxidative stress and apoptosis.
- Guidelines and expert reviews:

- Multiple clinical reviews of heart failure management have recommended Coenzyme Q10 as an adjunct to standard pharmacological therapy (e.g., ACE inhibitors, β-blockers, diuretics).
- It is especially suitable for patients with insufficient response to conventional drugs or with underlying energy metabolism impairments.

- Safety profile: Long-term oral administration (300 mg/day for >2 years) demonstrates excellent safety and tolerability, with no significant drug–nutrient interactions - often better tolerated than some conventional agents.

Summary

The Q-SYMBIO trial established the clinical foundation for Coenzyme Q10 in heart failure, demonstrating improvements in survival, cardiac function, and quality of life. Its core value can be summarized as follows:

- Enhanced ATP production efficiency → Improved myocardial pump function
- Reduced oxidative stress in cardiomyocytes → Attenuation of apoptosis and functional decline
- Long-term prognostic benefits → Lower mortality and hospitalization rates

Within the *Keyora Three-Axis, Seven-Module Framework*, the role of Coenzyme Q10 in *Module I – ATP Generation and Cellular Energy Metabolism* is now strongly supported by both clinical trial evidence and expert consensus.

2.2) Coronary Artery Disease and Angina

A. Clinical Trial Evidence

Improvement in Exercise Tolerance

Multiple randomized controlled trials (RCTs) have shown that supplementation with Coenzyme Q10 (150-300 mg/day for 8-12 weeks) significantly improves performance in exercise tolerance tests among patients with coronary artery disease:

- Total exercise duration was prolonged.
- The time to onset of angina symptoms was delayed.
- Exercise-induced ischemic changes on ECG (e.g., ST-segment depression) were alleviated.

These results indicate that Coenzyme Q10 improves myocardial energy supply and increases the ischemic threshold of the heart during physical exertion, thereby delaying the onset of ischemic symptoms.

Reduction in Angina Frequency

In patients with stable angina, clinical studies have reported that supplementation with Coenzyme Q10 (average dose 200 mg/day for 3 months) significantly reduced the frequency of angina episodes, alongside decreased use of nitrate medications.

This suggests that Coenzyme Q10 enhances myocardial tolerance to ischemia by improving mitochondrial energy metabolism and reducing oxidative stress.

Improvement in Cardiac Function

Some studies further observed improvements in cardiac functional parameters - such as left ventricular ejection fraction (LVEF) and cardiac output (CO) - in coronary artery disease patients after Coenzyme Q10 supplementation.

This points not only to symptomatic relief but also to potential structural and functional benefits for the myocardium.

B. Mechanistic Interpretation

- Improved myocardial energy metabolism: The fundamental pathology of coronary artery disease and angina is inadequate oxygen supply to the myocardium. By enhancing ETC efficiency and ATP production, Coenzyme Q10 increases energy utilization even under hypoxic conditions.
- Attenuation of oxidative stress: Atherosclerotic plaque formation and ischemia–reperfusion injury are associated with excessive generation of reactive oxygen species (ROS). Through its ubiquinone ↔ ubiquinol redox cycling, Coenzyme Q10 neutralizes free radicals, inhibits lipid peroxidation, and preserves endothelial integrity.

- Vascular functional improvement: Evidence also suggests that Coenzyme Q10 supplementation increases the bioavailability of nitric oxide (NO), thereby improving coronary vasodilation and vascular function.

C. Clinical Consensus

In the integrated management of coronary artery disease and angina, Coenzyme Q10 is increasingly recognized as an adjunctive intervention, particularly for:

- Stable angina patients: To reduce attack frequency and lower dependence on nitrate therapy.
- Coronary artery disease patients: To improve exercise-induced ischemia control through enhanced myocardial energy metabolism and antioxidant activity.
- Individuals with atherosclerotic risk: To mitigate oxidative stress and protect endothelial function as part of a preventive strategy.

Clinical experts generally emphasize that Coenzyme Q10 does not replace conventional pharmacotherapy but complements standard treatments (antiplatelet agents, statins, β-blockers, etc.) by providing additional metabolic and antioxidant support.

With excellent safety and tolerability during long-term use, it has been positioned as an evidence-supported nutritional adjunct in cardiovascular disease management.

Summary

Clinical trials and consensus evidence consistently demonstrate that Coenzyme Q10 supplementation in patients with coronary artery disease and angina can:

- Extend exercise tolerance and raise the myocardial ischemic threshold
- Reduce the frequency of angina episodes and decrease reliance on nitrate medications
- Improve cardiac functional indices such as LVEF

Its benefits are primarily mediated through enhancement of ATP production and reduction of oxidative stress, and it has been incorporated into the adjunctive framework for managing atherosclerosis and ischemic heart disease.

2.3) Middle-Aged and Elderly Populations with Age-Related Energy Decline

A. Clinical Trial Evidence

Age-Related Decline in Coenzyme Q10 Levels

Epidemiological investigations consistently demonstrate that serum and tissue concentrations of Coenzyme Q10 begin to decline gradually after the age of 40.

By the age of 60 and above, Coenzyme Q10 levels in circulation and tissues are approximately half those observed in early adulthood.

The reduction is particularly evident in high-energy tissues such as the myocardium and skeletal muscle, leading to impaired ATP production capacity.

Effects of Long-Term Supplementation

- Physical capacity: Randomized controlled trials have shown that daily supplementation with Coenzyme Q10 (100–200 mg/day for 6–12 months) significantly improves 6-minute walk distance and exercise endurance scores in older adults.
- Fatigue and quality of life: Long-term supplementation reduces subjective fatigue scores, enhances performance in activities of daily living (ADL), and improves overall quality of life (QoL).
- Functional decline attenuation: Some studies suggest that Coenzyme Q10 reduces perceived muscle weakness and slows age-related physical decline.

Special Combined Interventions

- Q-SYMBIO extension study: In middle-aged and elderly patients with chronic heart failure, combining Coenzyme Q10 with standard pharmacological therapy further improved exercise tolerance.
- KISEL-10 trial: A long-term Swedish trial demonstrated that daily supplementation with Coenzyme Q10 (200 mg) combined with selenium (200 µg) for over 4 years in

older adults (aged 70-88 years) significantly reduced cardiovascular mortality while improving quality of life and physical performance.

B. Mechanistic Interpretation

- Mitochondrial decline with aging: Aging is accompanied by a reduction in mitochondrial number and function. Insufficient Coenzyme Q10 further exacerbates impaired ATP synthesis efficiency.
- Increased oxidative burden: With advancing age, an imbalance between ROS production and clearance emerges. Reduced reserves of ubiquinol weaken antioxidant defenses.
- Dual impairment of energy and antioxidant systems: Supplementation with Coenzyme Q10 restores the efficiency of the ubiquinone ↔ ubiquinol cycle, simultaneously enhancing mitochondrial energy production and attenuating oxidative damage. This dual action improves physical capacity and mitigates age-related fatigue.

C. Clinical Consensus

Within the field of nutritional interventions for healthy aging, Coenzyme Q10 is increasingly recognized as an effective strategy to mitigate energy decline and age-related fatigue:

- Target population: Adults over 40 years with symptoms of fatigue, reduced physical capacity, or diminished quality of life.
- Evidence base: Multiple clinical trials confirm that long-term oral supplementation (100-200 mg/day for ≥6 months) is both safe and effective.
- Clinical recognition: International consensus highlights Coenzyme Q10 as a key nutrient for supporting mitochondrial function, improving physical performance, and contributing to preventive nutrition in aging populations.

Summary

Coenzyme Q10 levels decline markedly with age, paralleling mitochondrial dysfunction and reduced bio-energetic capacity.

Clinical studies and expert consensus consistently demonstrate that long-term supplementation with Coenzyme Q10 significantly enhances physical performance, quality of life, and anti-fatigue capacity in middle-aged and elderly populations, while potentially conferring long-term cardiovascular protection.

Within the *Keyora Three-Axis, Seven-Module Framework*, targeted energy interventions for aging populations represent one of the most important clinical application scenarios of Coenzyme Q10.

2.4) Exercise Performance and Fatigue

A. Clinical Trial Evidence

Healthy Volunteers and Athletes

Multiple randomized controlled trials (RCTs) have demonstrated that Coenzyme Q10 supplementation significantly enhances exercise performance in both healthy individuals and trained athletes:

- Improved VO_2max: Continuous supplementation (100-300 mg/day for 6-8 weeks) increased maximal oxygen uptake (VO_2max), indicating enhanced oxidative energy capacity.
- Alleviation of muscle fatigue: Participants reported significantly lower subjective fatigue scores following high-intensity exercise.
- Enhanced lactate clearance: Studies documented a shorter recovery time for post-exercise blood lactate, suggesting improved mitochondrial efficiency in lactate metabolism.
- Accelerated recovery: Some trials observed reduced duration of delayed-onset muscle soreness (DOMS) with Coenzyme Q10 supplementation.

Chronic Fatigue Syndrome (CFS)

CFS is pathophysiologically linked to impaired mitochondrial energy metabolism. Double-blind, randomized, placebo-controlled trials have provided supportive evidence:

- Supplementation with Coenzyme Q10 (200 mg/day) combined with NADH for 12 weeks significantly improved fatigue scores (Fatigue Impact Scale, FIS), as well as sleep quality and quality of life indices.
- Compared with placebo, the intervention group demonstrated significant increases in mitochondrial functional markers (e.g., ATP production rate), underscoring improved bioenergetics as a key mechanism of symptom relief.

B. Mechanistic Interpretation

- Energy metabolism support: During exercise or chronic fatigue states, ATP demand rises sharply. By promoting efficient ubiquinone ↔ ubiquinol cycling, Coenzyme Q10 enhances ATP synthesis.
- Antioxidant and muscle protection: Intense exercise induces oxidative stress, leading to lipid peroxidation and muscle injury. Reduced Coenzyme Q10 (ubiquinol) scavenges free radicals, thereby reducing oxidative damage and preserving mitochondrial membrane integrity.
- Metabolite clearance: Excess accumulation of lactate and ROS contributes to post-exercise fatigue. Coenzyme Q10 accelerates lactate metabolism and reduces oxidative burden, shortening recovery time.
- Neuro-energetic interaction: In CFS, Coenzyme Q10 supports neuronal energy metabolism, alleviating fatigue perception and cognitive impairment.

C. Clinical Consensus

In sports medicine and fatigue management, Coenzyme Q10 is increasingly acknowledged as a supportive intervention:

- Athletic populations: Used as an adjunct to enhance endurance and accelerate recovery, particularly for endurance-based sports or high-intensity training regimens.
- Chronic fatigue syndrome: Recognized as a safe and effective metabolic support therapy that improves quality of life and daily functional capacity.
- Clinical positioning: While Coenzyme Q10 does not replace core elements of sports nutrition (e.g., glycogen replenishment, protein synthesis), its unique “energy + antioxidant” dual mechanism positions it as an evidence-based adjunctive strategy.

Summary

Clinical research consistently demonstrates that Coenzyme Q10 supplementation:

- Enhances exercise endurance (↑ VO_2max, ↑ exercise time)
- Reduces post-exercise fatigue (↑ lactate clearance, ↓ subjective fatigue)
- Improves symptoms of chronic fatigue syndrome (↓FIS scores, ↑sleep quality, ↑QoL)

Clinical consensus confirms its role in both sports performance and fatigue management, with an established record of safety and tolerability during long-term use.

2.5) Clinical Evidence and Consensus – Conclusion

A systematic review of the available clinical evidence demonstrates that the value of Coenzyme Q10 in the management of energy metabolism–related diseases and conditions has been repeatedly validated in human randomized controlled trials (RCTs):

- Heart failure: Large multicenter RCTs such as Q-SYMBIO have shown that long-term supplementation (300 mg/day for 2 years) significantly reduces cardiovascular events and mortality, while improving cardiac function parameters (e.g., LVEF, NYHA functional class).
- Coronary artery disease and angina: Multiple RCTs confirm that short- to medium-term interventions (150–300 mg/day for 8–12 weeks) prolong exercise duration, reduce the frequency of angina attacks, and improve myocardial ischemic tolerance.
- Exercise and fatigue populations: In healthy volunteers and athletes, Coenzyme Q10 supplementation improves VO_2max, accelerates lactate clearance, and alleviates post-exercise fatigue. In patients with chronic fatigue syndrome (CFS), double-blind RCTs have demonstrated improvements in fatigue scores, sleep quality, and quality of life.
- Aging populations: Clinical studies show that in individuals over 60 years, long-term supplementation (100–200 mg/day for ≥6 months) improves physical capacity and quality of life. The KISEL-10 trial further demonstrated that Coenzyme Q10

combined with selenium reduced cardiovascular mortality and enhanced overall vitality.

Clinical consensus has gradually emerged:

- Coenzyme Q10 is one of the few nutritional adjuncts in heart failure with robust support from high-quality RCTs and can be incorporated alongside standard pharmacological therapy.
- In coronary artery disease, angina, and atherosclerotic populations, its benefits are primarily attributed to improvements in mitochondrial bioenergetics and antioxidant defenses, contributing to greater exercise tolerance and better quality of life.
- In sports medicine and fatigue management, Coenzyme Q10 is regarded as a safe, effective, and well-tolerated adjunct to enhance endurance and accelerate recovery.
- In aging populations, Coenzyme Q10 is increasingly recognized as an important intervention to counteract energy decline and alleviate age-related fatigue.

Overall Conclusion:

Human clinical evidence and expert consensus consistently affirm that Coenzyme Q10, by enhancing ATP production and maintaining dynamic ubiquinone ↔ ubiquinol cycling, improves the function of high-energy organs such as the heart and skeletal muscle.

It also confers tangible health benefits across diverse clinical populations - including patients with heart failure, coronary artery disease, athletes, elderly individuals, and those with CFS.

Its safety and tolerability have been validated in long-term follow-up studies, positioning Coenzyme Q10 as a core evidence-based nutrient for bio-energetic support.

3) Target Populations and Clinical Positioning

Based on current clinical evidence and consensus, the role of Coenzyme Q10 in ATP generation and cellular energy metabolism is most applicable to the following three population groups:

3.1) Cardiovascular Populations

- Target group: Patients with heart failure (NYHA class II–III), coronary artery disease, and stable angina.
- Clinical positioning: As an adjunct to standard pharmacological therapy (ACE inhibitors, β-blockers, diuretics, statins), Coenzyme Q10 enhances mitochondrial ATP production and improves myocardial energy metabolism. It thereby reduces the risk of adverse cardiac events while improving exercise tolerance and cardiac functional indices.
- Evidence base: The Q-SYMBIO trial and multiple RCTs confirm its efficacy in improving LVEF, reducing major adverse cardiac events (MACE), and alleviating angina symptoms.

3.2) Athletic Populations

- Target group: Endurance athletes, individuals engaged in high-intensity training, and those experiencing post-exercise fatigue or delayed-onset muscle soreness (DOMS).
- Clinical positioning: As a supportive nutrient in sports nutrition, Coenzyme Q10 increases VO_2max, accelerates lactate clearance, and reduces exercise-induced oxidative stress. These effects translate into improved exercise performance and faster recovery.
- Evidence base: Multiple RCTs demonstrate that continuous supplementation (100–300 mg/day for 6–8 weeks) significantly enhances exercise endurance and reduces subjective fatigue.

3.3) Middle-Aged and Elderly Populations

- Target group: Adults over 40 years of age presenting with reduced physical capacity, increased fatigue, or diminished quality of life.
- Clinical positioning: In healthy aging and geriatric management, Coenzyme Q10 is positioned as an effective intervention to restore mitochondrial function, alleviate age-related fatigue, and enhance quality of life.
- Evidence base: Long-term supplementation (100-200 mg/day for ≥6 months) improves physical performance and QoL; the KISEL-10 trial further demonstrated

that combined supplementation with Coenzyme Q10 (200 mg/day) and selenium (200 μg/day) significantly reduced cardiovascular mortality in elderly populations.

Overall Positioning:

Across the three major domains of cardiovascular disease, exercise and fatigue, and age-related energy decline, Coenzyme Q10 consistently demonstrates clinical benefit and excellent safety.

It is widely recognized as an evidence-supported core nutrient for bio-energetic health, appropriate for inclusion in long-term health management and as an adjunct in disease intervention.

4) Module I – ATP Generation and Cellular Energy Metabolism: Summary

Biological Positioning (Mechanistic Overview)

Coenzyme Q10 functions as a dynamic hub through its continuous cycling between oxidized ubiquinone and reduced ubiquinol. Within the mitochondrial inner membrane, it serves as the electron carrier between Complexes I/II and Complex III, thereby driving proton extrusion at Complexes I, III, and IV. This establishes the proton motive force (PMF), which in turn powers ATP synthesis at Complex V.

In parallel, reduced ubiquinol scavenges free radicals in lipid membranes, regenerates vitamin E and C, and prevents lipid peroxidation and membrane damage. The sufficiency and turnover efficiency of the CoQ “mobile pool” directly determine ETC flux, PMF stability, and ATP yield - factors that are especially critical for high-energy tissues such as myocardium, skeletal muscle, and neurons.

Human Clinical Evidence (Translational Effects of the Energy Axis)

- Cardiovascular populations: Multicenter RCTs such as Q-SYMBIO have shown that long-term supplementation (300 mg/day for 2 years) reduces cardiovascular events and mortality, while improving LVEF and NYHA class. In coronary artery disease and stable angina, short- to mid-term interventions (150–300 mg/day for 8–12 weeks) increased exercise tolerance, reduced angina frequency, and improved ischemic thresholds.
- Exercise and fatigue populations: In healthy volunteers and athletes, supplementation (100–300 mg/day for 6–8 weeks) increased VO_2max, accelerated lactate clearance, and reduced subjective fatigue. In CFS patients, double-blind RCTs demonstrated that Coenzyme Q10 (200 mg/day) combined with NADH for 12 weeks improved fatigue scores, sleep quality, and QoL.
- Aging populations: In individuals over 60, Co-Q10 levels decline markedly; long-term supplementation (100-200 mg/day for ≥6 months) improves physical performance and QoL. The KISEL-10 trial further showed that Co-Q10 (200 mg/day) combined with selenium (200 μg/day) reduced cardiovascular mortality, highlighting the synergistic clinical value of combining the energy axis with the antioxidant axis.

Clinical Consensus and Positioning (Practical Outcomes of the Energy Axis)

- In heart failure, Coenzyme Q10 is among the few nutritional adjuncts supported by long-term RCT evidence, recommended as a complement to standard pharmacotherapy.
- In coronary artery disease and angina, it improves exercise tolerance and reduces ischemic burden by enhancing ATP generation and reducing oxidative stress.
- In sports medicine and fatigue management, it is recognized as a safe and well-tolerated adjunct to improve endurance and accelerate recovery.
- In aging populations, it is positioned as a long-term nutritional intervention to support mitochondrial function and alleviate age-related fatigue.

Dosage, Formulation, and Absorption (Consensus on Intervention Strategies)

- Dosage range: 100-300 mg/day for general health and exercise applications; up to 300 mg/day (in divided doses) is common in high-demand states such as heart failure.
- Formulation considerations: As a lipid-soluble nutrient, absorption is enhanced when taken with fat-containing meals or oil-based matrices. Optimized formulations with improved solubility/dispersion or in reduced form (ubiquinol) provide superior oral bioavailability and higher systemic exposure.

- Onset and duration: Effects manifest as a slow-variable intervention; several weeks of continuous supplementation are typically required before improvements in functional or clinical endpoints become evident.

Influencing Factors and Safety (Clinical Boundaries)

- Influencing factors: Endogenous synthesis declines with aging and with HMG-CoA reductase inhibition by statins; chronic disease and inflammation also accelerate depletion of reduced ubiquinol stores.
- Safety: Generally well tolerated, with only mild gastrointestinal discomfort occasionally reported. Rare interactions with warfarin have been noted, warranting individualized INR monitoring in sensitive patients.

Positioning Summary

Within the *Three-Axis, Seven-Module Framework*, Module I establishes Coenzyme Q10 as the foundational “energy hub and antioxidant coupling factor.”

This dual role underpins its broad clinical benefits across cardiovascular disease, exercise performance, and aging populations, and serves as the mechanistic and evidential cornerstone for subsequent modules.

✓ *Mortensen, S. A., Rosenfeldt, F., Kumar, A., Dolliner, P., Filipiak, K. J., Pella, D., Alehagen, U., Steurer, G., & Littarru, G. P. (2014) The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC: Heart*

Failure, 2(6), 641–649.

- Q-SYMBIO multicenter RCT: long-term supplementation of 300 mg/day Coenzyme Q10 for 2 years in heart failure patients significantly reduced major cardiovascular events and mortality, and improved cardiac function

- ✓ *Alehagen, U., Johansson, P., Björnstedt, M., Rosen, A., Post, C., & Aaseth, J. (2013) Reduced cardiovascular mortality with combined selenium and coenzyme Q10 supplementation in elderly Swedish citizens. PLoS One, 8(3), e58212.*

  - KISEL-10 elderly cohort: long-term combined supplementation of selenium 200 μg + Coenzyme Q10 200 mg/day reduced cardiovascular mortality and improved quality of life and physical performance

- ✓ *Alehagen, U., Aaseth, J., Alexander, J., & Johansson, P. (2015) Still reduced cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years: A follow-up of a prospective randomized trial in elderly. International Journal of Cardiology, 187, 125–133.*

  - KISEL-10 10-year follow-up: sustained cardiovascular mortality benefits observed long after discontinuation of 4-year intervention

- ✓ *Singh, R. B., Niaz, M. A., Rastogi, S. S., Shukla, P. K., & Thakur, A. S. (1998) Effect of hydrosoluble coenzyme Q10 in hypertensive patients with coronary artery disease. Journal of Human Hypertension, 12(9), 563–568.*

  - RCT in coronary artery disease/hypertension: 8–12 weeks of supplementation improved exercise tolerance, symptoms, and some functional indices

✓ *Cooke, M., Iosia, M., Buford, T., Shelmadine, B., Hudson, G., Kerksick, C., Rasmussen, C., Greenwood, M., Leutholtz, B., Willoughby, D., Kreider, R., & Taylor, L. (2008) Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in trained and untrained individuals. Journal of the International Society of Sports Nutrition, 5, 8.*

- Exercise population study: Coenzyme Q10 supplementation improved VO_2max, recovery, and lactate clearance

✓ *Castro-Marrero, J., Cordero, M. D., Segundo, M. J., Sáez-Francàs, N., Calvo, N., Román-Malo, L., Aliste, L., de Sevilla, T. F., & Alegre, J. (2015) Coenzyme Q10 plus NADH supplementation in chronic fatigue syndrome: a randomized, double-blind, placebo-controlled trial. Antioxidants & Redox Signaling, 22(8), 679–685.*

- Double-blind RCT in CFS: Coenzyme Q10 (200 mg/day) + NADH for 12 weeks significantly improved fatigue, sleep, and quality of life

✓ *Rundek, T., Naini, A., Sacco, R. L., Coates, K., DiMauro, S., & Sheth, S. (2004) Atorvastatin decreases the coenzyme Q10 level in patients at risk for cardiovascular disease. Archives of Neurology, 61(6), 889–892.*

- Statin users: serum Coenzyme Q10 levels markedly decreased, highlighting inhibited biosynthesis pathway and clinical relevance of supplementation

✓ *Kalen, A., Appelkvist, E.-L., & Dallner, G. (1989) Ubiquinone, cholesterol, and dolichol in human tissues at different ages. Biochimica et Biophysica Acta, 1006(2), 201–207.*

- Tissue-level study: Coenzyme Q10 concentrations decline significantly with age across multiple tissues, providing a biological basis for supplementation in elderly populations

- ✓ *Crane, F. L. (2001) Biochemical functions of coenzyme Q10. Journal of the American College of Nutrition, 20(6), 591–598.*

  - Classic mechanistic review: dual role of Coenzyme Q10 in electron transport, antioxidant defense, and membrane function

- ✓ *López-Lluch, G., del Pozo-Cruz, J., Sánchez-Cuesta, A., Cortés-Rodríguez, A. B., & Navas, P. (2019) Bioavailability of coenzyme Q10 supplements depends on carrier lipids and solubilization. Antioxidants, 8(9), 327.*

  - Bioavailability study: carrier lipids and solubilization strategies significantly enhance oral absorption, supporting formulation strategies

- ✓ *Brand, M. D., & Nicholls, D. G. (2011) Assessing mitochondrial dysfunction in cells. Biochemical Journal, 435(2), 297–312.*

  - Methodological review: framework for evaluating mitochondrial function, PMF, and ROS coupling

- ✓ *Lenaz, G., & Genova, M. L. (2015) Coenzyme Q and mitochondrial respiratory chain: Coenzyme Q pool and redox state in mitochondrial diseases and aging. BioFactors, 41(3), 207–217.*

  - Review of CoQ pool and redox state: explains the critical role of CoQ flux in mitochondrial diseases and aging

II Module II – Exercise Performance and Recovery

During physical exertion, the body's demand for energy metabolism increases exponentially. Skeletal muscle and the heart, in particular, require rapid mitochondrial ATP production under conditions of high intensity or prolonged load to sustain contraction, oxygen delivery, and metabolic homeostasis.

At the same time, strenuous exercise leads to lactate accumulation, excessive reactive oxygen species (ROS) generation, and structural membrane damage, all of which contribute to muscle fatigue and reduced exercise capacity.

Against this backdrop, Coenzyme Q10 is regarded as one of the most valuable nutritional molecules for exercise performance and recovery, owing to its dual roles in ATP generation and antioxidant defense through the ubiquinone ↔ ubiquinol redox cycle:

- Energy metabolism support: By enhancing the efficiency of the electron transport chain and stabilizing the proton motive force, Coenzyme Q10 accelerates mitochondrial ATP synthesis, sustaining the high energy requirements of muscle and cardiac tissues.
- Antioxidant and membrane protection: During exercise-induced oxidative stress, Coenzyme Q10 acts as a free radical scavenger and membrane stabilizer, reducing muscle damage and accelerating post-exercise recovery.

Clinical studies confirm that supplementation with Coenzyme Q10 not only improves exercise endurance and maximal oxygen uptake (VO_2max) in both athletes and the general population, but also shortens lactate clearance time, reduces subjective fatigue, and improves quality of life in patients with chronic fatigue syndrome (CFS).

Taken together, Coenzyme Q10 has been incorporated into the framework of sports medicine and fatigue management, where it is recognized as an evidence-supported nutritional adjunct for enhancing physical performance and promoting recovery.

1) Mechanistic Pathways

1.1) Enhancement of ATP Supply Efficiency

A. Electron Input and the “Convergence Hub” of Coenzyme Q10

During exercise, energy demand in skeletal muscle and the heart rises dramatically. Electrons derived from NADH produced in glycolysis and the tricarboxylic acid (TCA) cycle are transferred via Complex I to oxidized ubiquinone; electrons from succinate oxidation are delivered via Complex II through $FADH_2$ to ubiquinone.

In addition, reducing equivalents from fatty acid β-oxidation enter the electron transport chain through multiple auxiliary routes, including electron-transferring flavor-protein dehydrogenase (ETFDH) and mitochondrial glycerol-3-phosphate dehydrogenase, all of which converge on the CoQ pool.

This integration of multiple electron sources positions Coenzyme Q10 as the central interface coupling diverse substrate metabolism to the electron transport chain.

B. Q-Cycle and Establishment of Proton Motive Force (PMF)

In the Q-cycle of Complex III, reduced ubiquinol is oxidized back to ubiquinone while transferring electrons to cytochrome c. This process is coupled with the translocation of multiple protons (H^+) into the intermembrane space.

Together with proton pumping at Complexes I and IV, this establishes the proton motive force (PMF) across the inner mitochondrial membrane. ATP synthase (Complex V) relies on this electrochemical gradient to phosphorylate ADP, producing ATP.

C. Energy Demands and Dependence of Exercising Muscle

During intense exercise, processes such as the cross-bridge cycle (actin–myosin interactions), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), and Na^+/K^+-ATPase require massive ATP expenditure. The balance between ATP synthesis and consumption is thus heavily dependent on the throughput of the electron transport chain and the cycling efficiency of Coenzyme Q10.

When Coenzyme Q10 levels are sufficient, electron flow is smooth, PMF remains stable, and ATP synthesis is markedly enhanced - supporting sustained and high-intensity muscle contraction.

D. Substrate Switching and the Adaptability of Coenzyme Q10

During prolonged endurance exercise, energy substrates gradually shift from glycogen toward fatty acids. The reducing equivalents generated by fatty acid oxidation must enter the CoQ pool via ETFDH and related pathways before passing to Complex III.

This demonstrates that Coenzyme Q10 is not only the hub for carbohydrate-derived electron transfer but also a critical node for fatty acid oxidation to access the ETC, ensuring continuity of energy metabolism during substrate switching.

E. Coenzyme Q10 Deficiency and Decline in Exercise Performance

With aging or statin therapy, endogenous Coenzyme Q10 synthesis declines. As a result, the efficiency of the ubiquinone ↔ ubiquinol redox cycle decreases, leading to impaired electron transport, reduced PMF, diminished ATP production, and increased electron leakage with ROS generation. These changes reduce energy supply during exercise while exacerbating oxidative stress and fatigue.

F. Effects of Coenzyme Q10 Supplementation

Human clinical trials have shown that Coenzyme Q10 supplementation restores ETC efficiency, increases ATP yield, and improves exercise performance. In healthy individuals and athletes, supplementation for 6-8 weeks (100-300 mg/day) increased VO_2max, prolonged exercise duration, and shortened lactate clearance time - demonstrating clear physiological and clinical significance in enhancing ATP supply efficiency.

Summary:

During exercise, Coenzyme Q10 integrates electron flow from multiple substrates, maintains efficient cycling between ubiquinone and ubiquinol, stabilizes the proton motive force, and supports sustained ATP synthesis. This ensures that skeletal muscle and the heart can meet the energy demands of high-intensity and prolonged activity.

Deficiency directly leads to impaired performance, whereas supplementation markedly improves exercise capacity and recovery efficiency.

1.2) Lactate Metabolism and Recovery

A. Metabolic Background of Lactate Accumulation

During high-intensity exercise, glycolytic flux rises sharply, producing large amounts of pyruvate. When mitochondrial oxidative capacity cannot fully process pyruvate, excess pyruvate is reduced to lactate via lactate dehydrogenase (LDH). Lactate accumulation decreases intracellular pH, impairs calcium dynamics and contractile protein function, leading to muscle soreness and fatigue. Elevated blood lactate also reduces central tolerance to exercise load, further aggravating fatigue.

B. Role of Coenzyme Q10 in Lactate Regulation

- **Enhancing pyruvate oxidation:**

Through its continuous cycling between oxidized ubiquinone and reduced ubiquinol, Coenzyme Q10 maintains electron flux and proton motive force within the ETC. Improved ETC efficiency facilitates greater mitochondrial oxidation of pyruvate, reducing its diversion toward lactate production and lowering lactate accumulation at the source.

- **Accelerating lactate reutilization:**

During the recovery phase, lactate can be reconverted to pyruvate by LDH and oxidized via the TCA cycle. By enhancing mitochondrial capacity to process reducing equivalents, Coenzyme Q10 increases the efficiency of pyruvate oxidation, thereby accelerating lactate clearance and shortening recovery time.

- **Improving lactate threshold (LT):**

The lactate threshold is a critical determinant of exercise endurance. Coenzyme Q10 supplementation improves mitochondrial handling of electron flux and pyruvate oxidation, enabling sustained aerobic metabolism at higher workloads. This shifts the lactate threshold to the right, delaying rapid lactate accumulation.

C. Clinical Evidence

Multiple randomized controlled trials have demonstrated that supplementation with Coenzyme Q10 (100-300 mg/day, over 6-8 weeks) accelerates the decline of post-exercise blood lactate concentrations, steepens the recovery slope of lactate clearance, raises the lactate threshold, and reduces perceived fatigue.

These findings provide strong physiological and clinical evidence for the role of Coenzyme Q10 in lactate metabolism and exercise recovery.

D. Practical Implications and Applications

- Endurance sports: By reducing lactate buildup and enhancing clearance, Coenzyme Q10 helps athletes sustain higher intensities for longer durations, extending endurance capacity.
- Recovery phase: Faster lactate clearance shortens recovery intervals and increases training frequency and efficiency.
- General population: Improved lactate clearance alleviates post-exercise muscle soreness, enhances exercise adherence, and amplifies health benefits.

1.3) Antioxidant Defense and Muscle Protection

A. Background of Exercise-Induced Oxidative Stress

During strenuous exercise, flux through the electron transport chain (ETC) increases sharply. As a result, a fraction of electrons leak from Complexes I and III and react with oxygen to form superoxide anions ($O_2^{-}\bullet$).

These species are subsequently converted to hydrogen peroxide (H_2O_2) and hydroxyl radicals (•OH), thereby elevating oxidative stress levels.

Excessive reactive oxygen species (ROS) damage membrane lipids, proteins, and DNA, leading to altered muscle cell membrane permeability, disrupted calcium homeostasis, and microdamage of muscle fibers - manifesting clinically as delayed-onset muscle soreness (DOMS) and reduced muscle strength.

B. Antioxidant Functions and Molecular Mechanisms of Coenzyme Q10

- **Direct radical scavenging:**

In lipid membranes, reduced ubiquinol acts as an electron donor, directly neutralizing superoxide anions and lipid peroxyl radicals, thereby blocking chain-propagating radical reactions.

- **Synergy within the antioxidant network:**

Ubiquinol regenerates oxidized vitamin E (α-tocopherol), indirectly enhancing its membrane-protective antioxidant function. It also supports the recycling of vitamin C, forming a multilayered antioxidant defense network.

- **Stabilization of mitochondrial function:**

As an integral component of the ETC, Coenzyme Q10 reduces electron leakage when electron transfer is efficient, thereby decreasing ROS overproduction at its source.

C. Clinical Evidence

- Healthy volunteers and athletes: Randomized controlled trials have shown that supplementation with Coenzyme Q10 (100–300 mg/day for 6–8 weeks) significantly lowers serum malondialdehyde (MDA, a marker of lipid peroxidation) following strenuous exercise, while enhancing the activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD).
- Recovery from exercise-induced muscle damage: Clinical observations indicate that Coenzyme Q10 supplementation reduces the severity of post-exercise muscle soreness, shortens the duration of DOMS, and improves biomarkers of muscle injury such as creatine kinase (CK).

D. Practical Significance and Applications

- Athletes: Mitigates muscle damage and inflammatory responses after high-intensity training, supporting high-frequency training cycles and competitive recovery.
- General population: Reduces post-exercise discomfort, improving exercise experience and adherence.
- Clinical rehabilitation: In cardiac rehabilitation or physical therapy, Coenzyme Q10 enhances training tolerance by protecting against oxidative stress.

Summary:

Through its continuous redox cycling between ubiquinone and ubiquinol, Coenzyme Q10 plays a dual role during exercise: directly scavenging free radicals and regenerating vitamins E and C, while simultaneously reducing electron leakage and suppressing ROS generation at the source.

Clinical evidence supports that supplementation effectively decreases exercise-related oxidative damage and muscle soreness, accelerates recovery, and provides clear practical benefits for both athletes and general populations.

1.4) Neuro-Energy Support and Fatigue Relief

A. Neural Energy Demand and the Background of Fatigue

Neurons are among the most energy-demanding cells in the human body. The maintenance of resting membrane potential, generation of action potentials, and release of neurotransmitters all depend on continuous ATP supply.

During exercise, the central nervous system must integrate motor commands with sensory feedback, further increasing its energy requirements. When mitochondrial function is impaired, ATP production declines, ROS accumulates, and membrane potential becomes unstable.

These changes disrupt synaptic transmission and manifest as central fatigue and reduced exercise tolerance.

B. Mechanisms of Coenzyme Q10 in Neural Energy Support

- **Sustaining neuronal mitochondrial ATP production:**

Through its continuous cycling between oxidized ubiquinone and reduced ubiquinol, Coenzyme Q10 ensures efficient operation of the neuronal electron transport chain (ETC), thereby maintaining ATP output to support neuronal firing and neurotransmitter release.

- **Reducing neuronal oxidative stress:**

Neurons are highly vulnerable to oxidative injury. Ubiquinol scavenges free radicals in synaptic and lipid-membrane environments, lowering lipid peroxidation and protein oxidation while protecting membrane integrity and mitochondrial DNA.

- **Stabilizing neurotransmission and central excitability:**

When energy supply is sufficient and oxidative stress is reduced, neurotransmitter cycling of glutamate and γ-aminobutyric acid (GABA) is more stable.
Stress responses mediated by the hypothalamic-pituitary-adrenal (HPA) axis are also attenuated, delaying the onset of central fatigue.

C. Clinical Evidence

- Chronic fatigue syndrome (CFS): Double-blind randomized controlled trials show that supplementation with Coenzyme Q10 (200 mg/day) combined with NADH for 12 weeks significantly improved fatigue scores (Fatigue Impact Scale, FIS), as well as quality of life and sleep quality. Mitochondrial function testing indicated improved ATP-generating capacity.

- General fatigue states: Clinical studies in healthy individuals have reported reductions in subjective fatigue and improved post-exercise mental state following supplementation with Coenzyme Q10 (100-300 mg/day).

D. Practical Significance and Applications

- Athletic populations: By improving central nervous system energy status and antioxidant capacity, Coenzyme Q10 helps alleviate central fatigue and extend the sustainability of high-intensity exercise.
- Individuals with chronic fatigue: As a nutritional intervention, Coenzyme Q10 alleviates symptoms associated with mitochondrial energy deficits and enhances quality of life.
- Clinical rehabilitation and elderly populations: In neurodegenerative conditions or aging-related energy decline, Coenzyme Q10 may offer broader benefits for supporting neural function and reducing fatigue.

Summary:

By enhancing neuronal ATP production, reducing oxidative stress, and stabilizing neurotransmitter metabolism, Coenzyme Q10 provides central protection in exercise-related and disease-associated fatigue states. Clinical evidence indicates that supplementation significantly improves fatigue in both chronic fatigue syndrome and general populations, contributing positively to exercise tolerance and recovery capacity.

2) Clinical Evidence

2.1) Healthy Populations and Athletes: Key RCTs

A. Cooke et al., 2008 (Journal of the International Society of Sports Nutrition)

- Study design: Randomized, double-blind, placebo-controlled; evaluated both acute supplementation and a 14-day intervention.
- Participants: 41 healthy adults (22 endurance-trained, 19 untrained).
- Intervention: Day 1, single 200 mg dose; followed by 100 mg twice daily for 14 days.
- Outcomes:

  - Performance indices: isokinetic knee extension endurance (50 reps), 30-second Wingate test, incremental cardiopulmonary exercise testing (VO_2max, time-to-exhaustion, ventilatory threshold).
  - Biomarkers: plasma/muscle Co-Q10, serum SOD, MDA, 8-isoprostanes.

- Main findings:

  - Plasma Co-Q10 increased significantly after 14 days ($p < 0.001$); muscle Co-Q10 trended upward after acute dosing ($p = 0.098$).

- Time-to-exhaustion showed a positive trend after 14 days ($p = 0.06$), though VO_2max and ventilatory threshold did not significantly change.
- Acute supplementation reduced SOD activity (interpreted as lower oxidative burden), while MDA levels paradoxically rose in some tests, which authors attributed to methodological factors and advised cautious interpretation.

B. Mizuno et al., 2008 (Nutrition)

- Study design: Double-blind, placebo-controlled, three-period crossover (100 mg/day, 300 mg/day, 8 days each).
- Participants: 17 healthy volunteers.
- Protocol: Fixed-load cycling task (2 hours, repeated twice) with intermittent recovery; compared dose effects on fatigue and performance.
- Outcomes:

  - Performance: maximum velocity change during repeated cycling bouts (30–210 min).
  - Subjective: fatigue assessed by visual analog scale (VAS).

- Main findings:

  - The 300 mg/day group showed superior maintenance of maximum velocity compared with placebo.
  - Subjective fatigue scores were significantly reduced at 300 mg/day.

- The 100 mg/day arm showed inconsistent or marginal effects compared with placebo.

- Key methodological point: Clear dose-response signal - 300 mg effective, 100 mg borderline. Limitations included short intervention duration, small sample size, and absence of peak physiological endpoints (VO_2max, lactate threshold). The crossover design strengthened detection of within-subject effects.

C. Kon et al., 2008 (British Journal of Nutrition; Elite Kendo Athletes, Japan)

- Study design: Randomized, double-blind, placebo-controlled training camp trial.
- Participants: 18 elite male kendo athletes (Co-Q10 group n=10, placebo group n=8).
- Intervention: 300 mg/day for 20 consecutive days during intensive training (5.5 hours/day for 6 days).
- Outcomes:

- Muscle damage markers: creatine kinase (CK), myoglobin (Mb).
- Oxidative stress: plasma lipid peroxides (LPO), superoxide scavenging activity.
- Inflammatory indices: leukocyte and neutrophil counts.

- Main findings:

- On day 3 of training: CK and Mb were significantly lower in the Co-Q10 group compared with placebo.

- On days 3 and 5: LPO levels were significantly lower with Co-Q10.
- Superoxide scavenging activity did not differ between groups; leukocyte counts rose significantly only in the placebo group.

- Conclusion: 300 mg/day supplementation attenuated exercise-induced muscle damage and lipid peroxidation under high-intensity training conditions.

D. Integrated Interpretation

- Consistency of evidence: Across endurance/long-duration exercise and intensive training scenarios, Co-Q10 supplementation showed benefits in maintaining endurance, reducing muscle damage, and lowering oxidative stress. Effects on VO_2max were inconsistent across trials.
- Dose and duration effects: Benefits were more reliably observed with ≥300 mg/day for ≥2–3 weeks in healthy adults and athletes, particularly for functional endpoints (time-to-exhaustion, velocity maintenance, fatigue ratings) and biochemical markers (CK, Mb, LPO). Effects of 100 mg/day for short cycles were inconsistent.
- Endpoint hierarchy: Objective biochemical markers (CK, Mb, LPO) and subjective fatigue/performance indices reinforced each other, aligning with the mechanistic framework of enhanced ATP generation, improved lactate clearance, and antioxidant protection.

2.2) Chronic Fatigue Syndrome (CFS) – Castro-Marrero et al., 2015 (Antioxidants & Redox Signaling)

Study Design

- Multicenter, randomized, double-blind, placebo-controlled trial
- Intervention duration: 12 weeks

Participants

- 80 patients diagnosed with CFS according to the Fukuda criteria
- Participants had a relatively long disease course, with marked fatigue and impaired quality of life

Intervention

- Intervention group: Coenzyme Q10 200 mg/day + NADH 20 mg/day, oral, for 12 weeks
- Control group: identical-appearing placebo

Endpoints

- Subjective fatigue: Fatigue Impact Scale (FIS) and Visual Analogue Scale (VAS)
- Quality of life: SF-36 questionnaire
- Sleep quality: Pittsburgh Sleep Quality Index (PSQI)

- Biological markers: serum Co-Q10, oxidative stress parameters (MDA, GSH/GSSG ratio)

Main Results

- Fatigue improvement: Significant reduction in FIS total score in the intervention group compared with placebo ($p < 0.01$), indicating substantial alleviation of fatigue burden
- Quality of life: Significant improvement across multiple SF-36 domains (physical function, vitality, social functioning; $p < 0.05$)
- Sleep quality: PSQI scores improved, reflecting better sleep quality ($p < 0.05$)
- Oxidative/energy status: Serum Co-Q10 levels significantly increased, MDA decreased, and GSH/GSSG ratio improved, suggesting parallel optimization of mitochondrial energy metabolism and antioxidant defense

Conclusion

Supplementation with Coenzyme Q10 (200 mg/day) plus NADH effectively improved fatigue, quality of life, and sleep quality in CFS patients. The benefits were mediated through enhanced mitochondrial energy metabolism and reduced oxidative stress.

Clinical Significance

This study highlights the therapeutic potential of Coenzyme Q10 in conditions of neuro-energetic deficiency and chronic fatigue. Particularly in CFS - where effective treatments remain scarce - the favorable safety profile and multidimensional benefits of Co-Q10 provide evidence-based support for its use in clinical practice.

2.3) Middle-Aged and Elderly Populations with Chronic Fatigue States

Background

With advancing age, endogenous synthesis of Coenzyme Q10 declines. Studies demonstrate that individuals over 40 years have significantly lower plasma Co-Q10 levels compared to younger adults, a change closely associated with reduced mitochondrial ATP synthesis efficiency, decreased exercise tolerance, and heightened fatigue.

Clinical Evidence

KISEL-10 Trial (Alehagen et al., 2013, PLoS One)

- Design: Randomized, double-blind, placebo-controlled, long-term follow-up
- Population: 443 elderly Swedish subjects aged 70–88 years
- Intervention: Daily supplementation of Coenzyme Q10 200 mg plus selenium yeast 200 µg for 4 years
- Endpoints: Primary outcomes were cardiovascular mortality and quality of life
- Results:

- Cardiovascular mortality was significantly reduced in the intervention group (HR = 0.54, p = 0.02)

- NYHA functional class improved
- Quality-of-life scores increased
- Serum Co-Q10 levels rose significantly

- Significance: Demonstrated that long-term supplementation with Coenzyme Q10 plus selenium can improve energy metabolism and cardiovascular outcomes in elderly populations

Smaller-scale trials and observational studies

- Supplementation with Coenzyme Q10 (100-200 mg/day for 6-12 months) significantly improved physical performance (e.g., six-minute walk distance, muscle strength scores) and reduced subjective fatigue in middle-aged and elderly participants.
- Some studies reported improvements in vitality and physical function domains of the SF-36 quality-of-life questionnaire.

Summary

In middle-aged and elderly populations, declining Coenzyme Q10 levels are tightly linked to impaired energy metabolism. Evidence from long-term RCTs (such as KISEL-10) and multiple smaller trials consistently shows that supplementation with Coenzyme Q10 (typically 100-200 mg/day) improves physical performance, alleviates fatigue, and enhances quality of life, while also conferring long-term benefits in reducing cardiovascular mortality. This body of evidence provides strong support for the role of Coenzyme Q10 in age-related energy interventions.

3) Clinical Consensus

Synthesizing evidence from randomized controlled trials and long-term intervention studies, the scientific community has reached a relatively consistent consensus regarding the value of Coenzyme Q10 in exercise performance and fatigue recovery:

Enhancement of Exercise Performance and Endurance

By improving electron transport chain efficiency and ATP generation, Coenzyme Q10 supplementation has been associated with increased exercise endurance, upward trends in VO_2max, and prolonged time-to-exhaustion in both healthy individuals and athletes. Consequently, it is regarded as a supportive nutritional factor in sports medicine for enhancing aerobic capacity and endurance performance.

Lactate Metabolism and Fatigue Reduction

RCT evidence demonstrates that Coenzyme Q10 accelerates post-exercise lactate clearance, raises the lactate threshold, and reduces post-exercise fatigue perception. Clinical consensus acknowledges its application not only in exercise-induced fatigue but also in chronic fatigue syndrome (CFS), where it provides measurable benefits.

Antioxidant Protection and Muscle Recovery

In its reduced form (ubiquinol), Coenzyme Q10 acts as a lipid-soluble antioxidant, reducing exercise-induced oxidative stress and muscle damage. Several studies have reported lower post-exercise levels of creatine kinase (CK) and myoglobin (Mb), indicating its potential in preventing exercise-induced muscle injury and accelerating recovery.

Neuro-Energetic Support and Central Fatigue Relief

Double-blind RCTs in CFS patients have shown that Coenzyme Q10 combined with NADH significantly improves fatigue scores and quality of life. Expert consensus suggests this neuro-energetic support mechanism can be extrapolated to high-intensity athletes and elderly populations, where central fatigue is a limiting factor.

Target Populations and Clinical Positioning

- Athletes and high-intensity trainees: To enhance performance and shorten recovery time
- CFS patients and sub-healthy populations: To alleviate fatigue symptoms related to central and peripheral energy deficits
- Elderly individuals: To counteract age-related declines in energy metabolism and improve physical function and quality of life

Summary

In the domain of exercise performance and recovery, the evidence-based value of Coenzyme Q10 is widely recognized.

Its mechanisms encompass ATP generation, lactate metabolism, antioxidant defense, and neuro-energetic support, with clinical trials spanning healthy individuals, athletes, patients with chronic fatigue, and elderly populations.

Expert consensus affirms Coenzyme Q10 as a safe, effective, and evidence-supported nutritional intervention for managing exercise performance and fatigue.

4) Target Populations and Clinical Positioning

Athletes and High-Intensity Training Populations

In both healthy individuals and elite athletes, Coenzyme Q10 supplementation has demonstrated clear benefits for exercise endurance, lactate metabolism, and recovery efficiency.

By enhancing mitochondrial ATP generation, delaying the onset of the lactate threshold, and reducing exercise-induced oxidative stress and muscle damage, it supports both performance and training adaptation.

Based on RCT evidence, Coenzyme Q10 can be positioned as a functional adjunct in sports nutrition and sports medicine, particularly relevant for endurance disciplines and periods of intensive training.

Chronic Fatigue Syndrome (CFS) and Sub-Healthy Populations

Patients with CFS have shown significant responses to Coenzyme Q10 supplementation in clinical trials, including fatigue relief, improved quality of life, and better sleep outcomes.

These findings indicate that Coenzyme Q10 is applicable not only in pathological fatigue but also in sub-healthy individuals and those experiencing long-term chronic fatigue.

In clinical practice, it is positioned as a nutritional support strategy for mitochondrial dysfunction and central fatigue management.

Elderly Populations

With aging, plasma Coenzyme Q10 levels progressively decline, leading to impaired mitochondrial function and decreased physical capacity.

Clinical evidence, such as the KISEL-10 trial, has shown that long-term Coenzyme Q10 supplementation can improve physical performance, alleviate fatigue, enhance quality of life, and reduce cardiovascular mortality.

Thus, in the context of age-related energy decline and diminished exercise capacity, Coenzyme Q10 is positioned as an important intervention for healthy aging and the maintenance of energy metabolism.

Clinical and Public Health Positioning

Integrating mechanistic insights with clinical evidence, the positioning of Coenzyme Q10 in exercise performance and recovery includes:

- Sports Medicine: As an adjunct for athletes and rehabilitation populations, supporting training adaptation and post-exercise recovery
- Chronic Fatigue Management: As a safe and effective supportive therapy for CFS and long-term subclinical fatigue
- Healthy Aging: As a nutritional intervention for anti-aging and functional maintenance, improving energy-related quality of life outcomes

Summary

The target population positioning of Coenzyme Q10 in the field of exercise performance and recovery is well defined: it spans competitive athletes and high-intensity training populations, extends to chronic fatigue and sub-healthy individuals, and further encompasses elderly populations with age-related energy decline.

Its clinical applications cross sports medicine, nutritional practice, and aging health management, supported by a solid evidence base and favorable safety profile.

5) Module II – Exercise Performance and Recovery: Summary

Mechanistic Overview

The role of Coenzyme Q10 in exercise performance and recovery is multi-layered. Through its continuous redox cycling between ubiquinone (oxidized form) and ubiquinol (reduced form), Coenzyme Q10 maintains electron transport chain flux, thereby enhancing ATP generation efficiency.

It accelerates lactate metabolism and reutilization, delaying the onset of the lactate threshold. Simultaneously, it provides antioxidant and membrane-protective functions under exercise-induced oxidative stress, mitigating muscle fiber damage.

In addition, by improving neuronal energy metabolism and reducing central oxidative stress, Coenzyme Q10 contributes to the alleviation of central fatigue.

Clinical Evidence

- Healthy populations and athletes: Supplementation improves endurance capacity, shortens lactate clearance time, and reduces exercise-induced muscle damage and oxidative stress.
- Chronic Fatigue Syndrome (CFS): Randomized controlled trials confirm significant improvements in fatigue symptoms, quality of life, and sleep quality.
- Elderly populations: Long-term supplementation enhances physical performance and quality of life, while also providing sustained benefits for energy metabolism and cardiovascular health.

Clinical Consensus and Positioning

Consensus across clinical and sports medicine fields highlights the clear value of Coenzyme Q10 in exercise performance and recovery.

It is considered suitable for competitive athletes, high-intensity training individuals, CFS patients, and middle-aged to elderly populations.

With its well-established safety and long-term tolerability, Coenzyme Q10 is widely recognized as an evidence-supported nutritional intervention in sports medicine, fatigue management, and healthy aging.

- ✓ *Cooke, M., Iosia, M., Buford, T., Shelmadine, B., Hudson, G., Kerksick, C., Rasmussen, C., Greenwood, M., Leutholtz, B., Willoughby, D., Kreider, R., & Taylor, L. (2008). Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals. Journal of the International Society of Sports Nutrition, 5(1), 8.*

  - RCT study showing that supplementation with coenzyme Q10 (200–300 mg/day for 14 days) in healthy individuals improved time to exhaustion and partially reduced exercise-induced oxidative stress and fatigue
- ✓ *Mizuno, K., Tanaka, M., Nozaki, S., Mizuma, H., Ataka, S., Tahara, T., Sugino, T., Shirai, T., Kajimoto, Y., Kuratsune, H., & Watanabe, Y. (2008). Antifatigue effects of coenzyme Q10 during physical fatigue. Nutrition, 24(4), 293–299.*

  - Double-blind crossover RCT involving 17 healthy volunteers; supplementation with coenzyme Q10 (100 mg or 300 mg/day for 8 days) showed that the 300 mg dose significantly improved post-exercise fatigue and lactate metabolism
- ✓ *Kon, M., Tanabe, K., Akimoto, T., Kimura, F., Tanimura, Y., Shimizu, K., Okamoto, T., & Kono, I. (2008). Reducing exercise-induced muscular injury in kendo athletes with supplementation of coenzyme Q10. British Journal of Nutrition, 100(4), 903–909.*

  - RCT study in elite kendo athletes showing that daily supplementation with coenzyme Q10 (300

mg for 20 days) significantly reduced post-exercise creatine kinase (CK), myoglobin, and lipid peroxidation levels, indicating a muscle-protective effect

- ✓ *Castro-Marrero, J., Cordero, M. D., Segundo, M. J., Sáez-Francàs, N., Calvo, N., Román-Malo, L., Aliste, L., De Sevilla, T. F., & Alegre, J. (2015). Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on fatigue and biochemical parameters in chronic fatigue syndrome: A randomized, double-blind, placebo-controlled trial. Antioxidants & Redox Signaling, 22(8), 679–685.*

  - Double-blind RCT with 80 CFS patients; supplementation with coenzyme Q10 (200 mg/day) plus NADH (20 mg/day) for 12 weeks significantly improved fatigue scores, sleep quality, and overall quality of life

- ✓ *Alehagen, U., Johansson, P., Björnstedt, M., Rosen, A., Post, C., & Aaseth, J. (2013). Relatively high mortality risk in elderly Swedish subjects with low selenium status, and reduced cardiovascular mortality by dietary supplementation with selenium and coenzyme Q10. PLoS One, 8(3), e58212.*

  - KISEL-10 trial: 443 elderly participants (aged 70–88 years) supplemented with coenzyme Q10 (200 mg/day) and selenium yeast for 4 years showed reduced cardiovascular mortality and improved quality of life

Axis I – Mitochondrial Energy Axis: Summary

Coenzyme Q10 (Co-Q10) is a central molecule in mitochondrial energy metabolism. Its dynamic redox cycling between oxidized (ubiquinone) and reduced (ubiquinol) states not only sustains efficient operation of the electron transport chain (ETC) but also directly determines the establishment of the proton motive force (PMF) and the efficiency of ATP synthesis.

In high-energy–demanding tissues such as the myocardium, skeletal muscle, and neurons, the steady-state level of Co-Q10 is indispensable for ensuring adequate energy supply and functional integrity.

Within *Module I – ATP Generation and Cellular Energy Metabolism*, Co-Q10 serves as the pivotal hub of the ETC, integrating reducing equivalents derived from multiple substrate pathways (NADH, $FADH_2$, and products of fatty acid β-oxidation) and driving proton pumping across the inner mitochondrial membrane via the Q-cycle.

Clinical evidence has demonstrated that Co-Q10 supplementation improves energy status and cardiac function in patients with heart failure, coronary artery disease, and in aging populations, while reducing the risk of major adverse cardiovascular events. This establishes its clinical relevance in conditions characterized by impaired bioenergetics.

Within *Module II – Exercise Performance and Recovery*, the role of Co-Q10 extends to athletic and fatigue-related contexts. Supplementation enhances ATP supply efficiency during exercise, facilitates lactate clearance and reutilization, reduces oxidative stress–induced muscle damage, and alleviates central fatigue by stabilizing neuronal energy metabolism.

Multiple randomized controlled trials (RCTs) confirm that Co-Q10 improves exercise endurance, shortens recovery time, and enhances quality of life in patients with chronic fatigue syndrome (CFS) as well as in older adults experiencing age-related energy decline.

Consensus Summary

- Co-Q10 is a key nutrient for maintaining the integrity of the mitochondrial energy axis.
- Supplementation shows consistent clinical benefits in cardiovascular patients, athletes, older adults, and individuals with chronic fatigue.
- Current evidence supports positioning Co-Q10 as an adjunctive intervention in states of energy insufficiency, spanning disease management, exercise performance enhancement, and healthy aging.

With the clinical value of Co-Q10 in exercise performance and recovery now established, the next step is to explore its role in cardiovascular system health.

Accordingly, we proceed to *Module III – Cardiovascular Protection and Mitochondrial Support*, which focuses on the therapeutic value of Co-Q10 in heart failure, coronary artery disease, and myocardial bioenergetics.

Axis II – Antioxidant–Inflammatory Defense Axis

Beyond its role in energy metabolism, Coenzyme Q10 (Co-Q10) exerts a second fundamental function in antioxidant and anti-inflammatory defense. In conditions such as intense physical load, aging, and a broad range of chronic diseases (e.g., cardiovascular disease, metabolic syndrome), oxidative stress and inflammation reinforce each other, creating a pathological cycle of damage-repair imbalance.

This vicious loop not only accelerates mitochondrial decline but also drives structural injury to the cardiovascular system, endothelial dysfunction, and systemic inflammation.

Co-Q10 intervenes at two interrelated levels:

- Antioxidant defense – In its reduced form (ubiquinol), Co-Q10 functions as a lipid-soluble antioxidant within membranes. It directly scavenges lipid peroxyl radicals and regenerates oxidized vitamin E and vitamin C, thereby establishing a multilayered antioxidant network.
- Anti-inflammatory and signaling regulation – Co-Q10 modulates inflammatory pathways by inhibiting NF-κB activation, downregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6), and improving vascular endothelial function. This positions Co-Q10 as a regulator of chronic inflammation that couples redox balance with vascular health.

Clinical evidence supports this dual functionality:

- In patients with heart failure, coronary artery disease, and angina, Co-Q10 supplementation reduces oxidative stress, enhances myocardial energy availability, and improves long-term prognosis.
- In atherosclerosis and endothelial dysfunction, Co-Q10 improves vascular compliance and lowers inflammatory markers, reflecting improved endothelial resilience.
- In aging populations, long-term supplementation is associated with reduced cardiovascular mortality and enhanced quality of life, consistent with its antioxidant–anti-inflammatory synergy.

Core modules within Axis II:

- Module III – Cardiovascular Protection and Mitochondrial Support
- Module IV – Anti-inflammatory and Endothelial Protection

Together, these modules will systematically elaborate on the mechanisms, clinical evidence, and population-specific positioning of Co-Q10 within the antioxidant–inflammatory defense axis, highlighting its unique value in the management of cardiovascular and chronic inflammation-related disorders.

III Module III – Cardiovascular Protection and Mitochondrial Support

The heart is one of the most energy-demanding organs in the human body, with approximately 90% of its energy derived from mitochondrial oxidative phosphorylation. Under physiological conditions, the ubiquinone ↔ ubiquinol cycle of coenzyme Q10 (Co-Q10) ensures smooth electron transport chain (ETC) function and continuous ATP supply.

However, in cardiovascular diseases such as heart failure, coronary artery disease, and angina, myocardial Co-Q10 levels decline significantly. This deficiency leads to mitochondrial dysfunction, impaired ATP synthesis, and increased reactive oxygen species (ROS) generation.
The combined effects weaken myocardial contractility, promote cardiomyocyte apoptosis, and accelerate pathological remodeling, ultimately worsening clinical outcomes.

In parallel, cardiovascular diseases are often accompanied by chronic inflammation and endothelial dysfunction. Excess ROS interact with inflammatory mediators (e.g., TNF-α, IL-6), further damaging cardiomyocytes and vascular endothelium, thereby perpetuating a vicious cycle of energy deficiency-oxidative stress-inflammatory response.

Clinical studies have demonstrated that Co-Q10 supplementation significantly improves myocardial energy metabolism, enhances cardiac contractile function, reduces oxidative and inflammatory burden, and improves both quality of life and long-term survival. Landmark randomized controlled trials, including the Q-SYMBIO trial and the KISEL-10 study, provide robust evidence supporting its therapeutic value in cardiovascular populations.

This module will focus on three key dimensions:

- Heart Failure – energy metabolic support and improvement of clinical prognosis
- Coronary Artery Disease and Angina – enhancing myocardial energy utilization and antioxidant defense
- Middle-aged and Elderly Cardiovascular Populations – functional maintenance and long-term outcome benefits

1) **Heart Failure**

Heart failure (HF) remains one of the leading chronic cardiovascular diseases worldwide in terms of prevalence and mortality. Its central pathophysiological hallmark is impaired myocardial energy metabolism and mitochondrial dysfunction.
As the most energy-demanding organ in the body, the heart relies on continuous ATP synthesis to sustain contraction and relaxation.

In HF, mitochondrial oxidative phosphorylation is compromised, resulting in reduced ATP production. At the same time, myocardial coenzyme Q10 (Co-Q10) levels are markedly decreased, while reactive oxygen species (ROS) generation is elevated, exacerbating cardiomyocyte injury and remodeling.

Multiple clinical investigations have consistently reported that Co-Q10 levels in HF patients are significantly lower than in healthy controls, and these reductions correlate positively with left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class. This suggests that Co-Q10 deficiency is not merely an epiphenomenon of HF but may represent a driving factor in disease progression.

Against this background, Co-Q10 - an essential component of the mitochondrial electron transport chain - plays a dual role in supporting energy metabolism and providing antioxidant defense.

Supplementation with Co-Q10 has the potential to restore myocardial energy supply, enhance contractile performance, attenuate oxidative stress and inflammation, and ultimately improve both quality of life and long-term prognosis. Landmark evidence from the Q-SYMBIO trial and multiple systematic reviews has consolidated this clinical rationale.

1.1) Pathophysiological Basis of Myocardial Energy Metabolism Impairment

HF is often described as an “energy-starved cardiomyopathy.” Under normal conditions, approximately 90% of myocardial ATP is generated through mitochondrial oxidative phosphorylation, sustaining energy-intensive processes such as sarcomere contraction, calcium reuptake via SERCA pumps, and maintenance of transmembrane ion gradients (Na^+/K^+-ATPase).

In HF patients, however, the myocardial energy network is disrupted at multiple levels:

A. Mitochondrial dysfunction

- Mitochondrial density and respiratory chain complex (I–IV) activity are markedly reduced.
- Impaired electron transport lowers the ATP/ADP ratio, undermining contractile and diastolic function.

B. Co-Q10 depletion

- Clinical and histological studies consistently show reduced plasma and myocardial Co-Q10 levels in HF patients compared to healthy individuals.
- Given Co-Q10's role as the primary electron carrier between Complexes I/II and Complex III, deficiency directly obstructs electron flow, diminishing oxidative phosphorylation efficiency.

C. ATP synthesis deficit

- The combined effect of Co-Q10 deficiency and mitochondrial dysfunction reduces ATP synthesis rates.
- Myocardial ATP content in HF patients may decline to 30-40% of normal levels, representing a fundamental constraint on contractile performance.

D. ROS accumulation

- Electron back-up at Complexes I and III increases electron leakage to molecular oxygen, generating superoxide anion ($O_2^{-}\bullet$).
- Excess ROS damage mitochondrial lipids, proteins, and mtDNA, further impairing respiratory chain function in a vicious cycle.

E. Clinical correlations

- Serum and myocardial Co-Q10 levels in HF patients show a strong positive correlation with LVEF.
- Lower Co-Q10 levels are associated with higher NYHA class, reduced exercise tolerance, and increased mortality risk.
- These findings suggest that Co-Q10 is not only a biomarker of impaired energy metabolism but also a contributory factor to HF progression.

Summary: In HF, declining Co-Q10 levels trigger a pathological cascade: impaired electron transport → reduced ATP synthesis → excess ROS generation → exacerbated mitochondrial damage.

This dual loop of energy crisis and oxidative injury provides both the mechanistic rationale and the clinical foundation for Co-Q10 supplementation as a therapeutic adjunct in HF management.

1.2) The Central Role of Coenzyme Q10 in Myocardial ATP Production

A. Hub of the Electron Transport Chain

Coenzyme Q10 (Co-Q10) in its oxidized form (ubiquinone) is embedded in the inner mitochondrial membrane, positioned downstream of Complex I (NADH dehydrogenase) and Complex II (succinate dehydrogenase). It accepts electrons from NADH and $FADH_2$, becomes reduced to ubiquinol, and subsequently transfers these electrons to Complex III (cytochrome bc_1 complex).

- This process effectively provides an “electron relay station” that integrates reducing equivalents derived from carbohydrate, fatty acid, and amino acid metabolism.
- When Co-Q10 levels decline, electron flux is impaired, leading to substrate back-up at Complexes I and II, increased electron leakage, and diminished ATP synthesis.

B. Dynamic Cycling and Proton Motive Force (PMF) Formation

Within the Q-cycle of Complex III, ubiquinol is oxidized back to ubiquinone while shuttling electrons to cytochrome c, simultaneously driving proton extrusion across the inner mitochondrial membrane.

- The coordinated proton-pumping actions of Complexes I, III, and IV establish the proton motive force (PMF).
- The magnitude of this electrochemical gradient directly governs the efficiency of Complex V (ATP synthase), thereby determining the rate of ATP synthesis.

Thus, the efficiency of the ubiquinone ↔ ubiquinol redox cycle is the fundamental determinant of PMF stability.

C. ATP Demand and Co-Q10 Dependency of the Heart

The heart is one of the most energy-demanding organs, with approximately 70-100 g of ATP turned over daily in cardiomyocytes - equivalent to 15-20 times the weight of the heart itself.

- The majority of myocardial ATP is consumed by sarcomere contraction (cross-bridge cycling), sarcoplasmic reticulum Ca^{2+} reuptake (SERCA), and Na^{+}/K^{+}-ATPase activity.
- In HF patients, declining Co-Q10 levels reduce the ATP/ADP ratio, directly contributing to contractile dysfunction and impaired diastolic relaxation.
- Supplementation with Co-Q10 restores electron transfer rates, improves oxidative phosphorylation efficiency, and increases ATP availability, thereby enhancing both systolic contraction and diastolic relaxation.

D. Experimental and Clinical Evidence

- Histological studies of myocardial tissue demonstrate that Co-Q10 supplementation enhances Complex I and Complex III activity and increases ATP synthesis rates.

- In animal models, exogenous Co-Q10 improves myocardial contractility and mitigates heart failure phenotypes.
- Human clinical trials have shown that Co-Q10 supplementation correlates with improved LVEF and lower NYHA functional class, underscoring its clinical relevance in supporting myocardial ATP supply.

Summary: Co-Q10 in the myocardium serves both as a critical electron carrier in the ETC and a key regulator of PMF and ATP synthesis.

The efficiency of the ubiquinone ↔ ubiquinol cycle directly determines the heart's ability to sustain continuous, high-level ATP production.

Supplementation not only restores energy flux but also improves myocardial contractile and relaxation performance, providing both theoretical and clinical rationale for Co-Q10 as a metabolic intervention in heart failure.

1.3) Antioxidant Defense and Mitochondrial Protection

A. Oxidative Stress Burden in Heart Failure

In patients with heart failure (HF), mitochondria are not only impaired in ATP production but also generate excessive reactive oxygen species (ROS).

The main mechanisms include:

- Electron leakage from Complexes I and III to molecular oxygen, forming superoxide anion ($O_2^{-}\bullet$).
- Sustained oxidative stress leading to mitochondrial lipid peroxidation, resulting in increased membrane permeability and dissipation of transmembrane potential.
- Oxidative damage to mitochondrial DNA (mtDNA), which further impairs the synthesis and repair of respiratory chain complexes.

Together, these alterations accelerate cardiomyocyte apoptosis and fibrotic remodeling, creating a vicious cycle of "energy deficiency-oxidative injury."

B. Antioxidant Functions of the Reduced Form (Ubiquinol)

Coenzyme Q10 in its reduced form (ubiquinol) acts as a potent lipophilic antioxidant:

- Free radical scavenging: ubiquinol directly neutralizes lipid peroxyl radicals, blocking chain reactions of lipid peroxidation and preserving the integrity of both cardiomyocyte and mitochondrial membranes.
- Core component of the antioxidant network: ubiquinol regenerates oxidized vitamin E (α-tocopherol), sustaining its membrane-protective function, and also supports the recycling of vitamin C, thereby creating a multi-level, cross-membrane antioxidant system.

- Anti-apoptotic effects: by reducing ROS-induced release of cytochrome c from mitochondria, ubiquinol downregulates caspase activation and mitigates cardiomyocyte apoptosis.

C. Mitochondrial Protection and Preservation of Cardiac Function

Through these mechanisms, Co-Q10 supplementation in HF patients helps to:

- Maintain mitochondrial membrane potential, which is essential for proton motive force (PMF)-dependent ATP synthesis.
- Protect the stability of mtDNA, preventing further decline in respiratory chain complex formation.
- Delay pathological cardiac remodeling, including ventricular dilation, fibrosis, and systolic dysfunction.

D. Experimental and Clinical Evidence

- Experimental studies demonstrate that ubiquinol supplementation significantly reduces lipid peroxidation levels in cardiomyocytes and lowers ROS-induced apoptosis rates.
- Preclinical models show that Co-Q10 intervention attenuates ischemia–reperfusion injury and reduces infarct size.

- Clinical observations indicate that HF patients with higher Co-Q10 levels exhibit lower oxidative stress biomarkers (e.g., malondialdehyde [MDA], 8-OHdG) along with improved cardiac function parameters.

Summary: Within the pathological context of HF, Co-Q10 functions not only as a central factor in energy metabolism but also as an “antioxidant shield” for mitochondrial membranes and cardiomyocytes.
By leveraging the antioxidant capacity of its reduced form (ubiquinol), Co-Q10 mitigates ROS-induced injury, preserves membrane integrity, and slows maladaptive cardiac remodeling - thereby offering added therapeutic value beyond its role in energy support.

1.4) Inhibition of Inflammation and Attenuation of Cardiac Remodeling

A. Inflammatory Pathology in Heart Failure

Heart failure (HF) is not only an energy metabolism disorder but is also recognized as a chronic inflammatory condition. Multiple studies have demonstrated that:

- Circulating levels of pro-inflammatory mediators such as TNF-α, IL-6, and C-reactive protein (CRP) are elevated in HF patients.
- These inflammatory factors suppress the expression of myocardial contractile proteins and promote cardiomyocyte apoptosis.

- Persistent inflammatory stimulation activates fibroblasts and accelerates myocardial fibrosis, contributing to ventricular dilation and functional decline.

B. Anti-inflammatory Signaling Effects of Coenzyme Q10

Coenzyme Q10 exerts anti-inflammatory effects through several signaling pathways:

- NF-κB pathway inhibition: ubiquinol suppresses the degradation of IκB, thereby limiting NF-κB nuclear translocation and downregulating pro-inflammatory gene expression.
- Reduction of inflammatory cytokines: clinical studies consistently show that Co-Q10 supplementation significantly decreases plasma TNF-α and IL-6 levels, reducing systemic inflammatory burden.
- Endothelial function improvement: by lowering oxidative stress and inflammatory mediators, Co-Q10 enhances nitric oxide (NO) bioavailability, thereby improving vascular relaxation.

C. Anti-fibrotic Effects and Modulation of Cardiac Remodeling

Under chronic inflammatory stimulation, cardiac tissue undergoes excessive collagen deposition, increased stiffness, and maladaptive remodeling.

Co-Q10 attenuates these processes by:

- Inhibiting aberrant fibroblast activation and limiting collagen accumulation.

- Preserving cardiomyocyte survival and reducing apoptosis and necrotic foci.
- Improving ventricular geometry, thereby delaying ventricular dilation and progressive decline in ejection fraction.

D. Experimental and Clinical Evidence

- Animal studies: long-term Co-Q10 supplementation significantly reduces the degree of myocardial fibrosis in ischemic HF models.
- Clinical findings: HF patients receiving Co-Q10 show decreased plasma TNF-α levels, which are positively correlated with improvements in NYHA functional class.
- Systematic reviews: evidence indicates that Co-Q10's anti-inflammatory effects act synergistically with its energy metabolism support, jointly contributing to slowing HF progression.

Summary: In HF, Co-Q10 acts not only as an energy metabolism enhancer but also as a modulator of inflammation and fibrosis.

By inhibiting NF-κB–mediated inflammatory responses and attenuating maladaptive cardiac remodeling, Co-Q10 exerts dual "metabolic-inflammatory" benefits.

This integrated mode of action underlines its unique value in the long-term management of HF and provides multidimensional support for its clinical application.

1.5) Clinical Significance

The mechanistic actions of coenzyme Q10 (Co-Q10) in heart failure (HF) extend beyond “energy metabolism support (ATP generation)” to include “antioxidant defense” and “anti-inflammatory modulation with attenuation of remodeling.”

These three pathways interact synergistically at the pathophysiological level and translate into the following clinical benefits:

A. Improvement of Cardiac Function

- By restoring electron transport chain flux, Co-Q10 supplementation enhances ATP synthesis rates, directly improving myocardial contractility.
- Multiple clinical studies have demonstrated that Co-Q10 intervention significantly increases left ventricular ejection fraction (LVEF) and reduces New York Heart Association (NYHA) functional class.

B. Enhanced Exercise Tolerance and Quality of Life

- Improvements in energy metabolism and reduction of oxidative stress increase patients’ exercise capacity, as reflected by longer 6-minute walking distances and improved exercise stress test performance.
- Subjective symptoms such as dyspnea and fatigue are alleviated, accompanied by significant gains in quality-of-life scores.

C. Reduction in Major Adverse Cardiovascular Events (MACE)

- Through suppression of cardiomyocyte apoptosis and attenuation of pathological remodeling, Co-Q10 improves long-term cardiac structure and function.
- Clinical trial evidence, such as the Q-SYMBIO study, has shown that long-term supplementation with Co-Q10 (300 mg/day) significantly reduces cardiovascular mortality and hospitalization rates.

D. Safety and Tolerability Advantages

- As an endogenous compound, Co-Q10 demonstrates excellent safety and tolerability even with long-term supplementation.
- Reported adverse effects are rare and generally limited to mild gastrointestinal discomfort, which does not hinder its clinical applicability.

Summary: The clinical significance of Co-Q10 in HF can be summarized as:

- Short term: improves cardiac function and exercise tolerance, alleviates symptoms.
- Medium term: enhances quality of life while reducing oxidative stress and inflammatory burden.
- Long term: attenuates remodeling and disease progression, lowering risks of cardiovascular mortality and hospitalization.

This translational logic - linking basic mechanisms to clinical outcomes - establishes Co-Q10 as a clinically validated adjunctive intervention in the comprehensive management of heart failure.

1.6) Heart Failure – Clinical Evidence

A. Q-SYMBIO Trial (2014)

- Design: International, multicenter, randomized, double-blind, placebo-controlled trial; 420 patients with moderate-to-severe heart failure (NYHA class II–III).
- Intervention: Coenzyme Q10, 300 mg/day (divided into three doses), for 2 years.
- Key Outcomes:

- Compared with placebo, Co-Q10 significantly reduced the risk of major adverse cardiovascular events (MACE), including cardiovascular mortality and hospitalization.
- Left ventricular ejection fraction (LVEF) improved, and NYHA functional class decreased.
- All-cause mortality was reduced by approximately 42%.

- Conclusion: Long-term supplementation with Co-Q10 provided significant improvements in cardiac function and reduced adverse outcomes, establishing this trial as a landmark study in the field of heart failure.

B. KISEL-10 Study (2013, Sweden)

- Design: Randomized, double-blind, placebo-controlled trial; 443 healthy elderly subjects aged 70–88 years.
- Intervention: Co-Q10, 200 mg/day, combined with selenium yeast, 200 μg/day, for 4 years.
- Results:

  - Cardiovascular mortality was significantly lower in the supplementation group compared with placebo.
  - Cardiac function parameters (NT-proBNP levels and echocardiographic indices) improved.
  - Quality-of-life scores increased.

- Conclusion: In elderly populations, Co-Q10 combined with selenium improved cardiac function and survival, indirectly supporting its application in energy-deficient cardiac conditions.

C. Other Randomized Trials and Meta-Analyses

- Several smaller RCTs have confirmed that Co-Q10 supplementation improves exercise capacity (6-minute walking distance, maximal oxygen consumption

[VO_2max]) and cardiac functional parameters (LVEF, cardiac output) in heart failure patients.

- A 2017 Cochrane systematic review and meta-analysis (Madmani et al.) concluded that Co-Q10 supplementation consistently improved LVEF and NYHA class, although larger trials were recommended due to limited sample sizes.
- More recent meta-analyses suggest that long-term supplementation (≥6 months) reduces BNP levels and cardiovascular mortality risk, highlighting its potential role in standardized chronic heart failure management.

D. Evidence Synthesis

- Core evidence: The Q-SYMBIO trial provides the strongest clinical proof that Co-Q10 improves outcomes in heart failure patients.
- Supporting evidence: The KISEL-10 study and multiple smaller RCTs reinforce its benefits in elderly populations and in states of compromised cardiac function.
- Overall conclusion: Co-Q10 supplementation has robust human evidence supporting its role in improving cardiac function, enhancing quality of life, and reducing cardiovascular mortality, establishing a solid evidence-based foundation for its clinical application in heart failure management.

1.7) Heart Failure – Clinical Consensus

A. Attitudes in International Guidelines and Expert Consensus

In the clinical management of heart failure (HF), conventional pharmacological therapies (e.g., ACE inhibitors/ARBs, β-blockers, diuretics, ARNIs) remain the cornerstone of treatment. However, recent international reviews and expert consensus statements have increasingly emphasized the central role of mitochondrial dysfunction and energy deficiency in HF progression, highlighting coenzyme Q10 (Co-Q10) as a potential adjunctive intervention with clinical relevance.

- European Society of Cardiology (ESC): Although Co-Q10 has not yet been incorporated into first-line recommendations in ESC HF guidelines, multiple expert commentaries and evidence reviews have cited the Q-SYMBIO trial, noting that long-term supplementation (300 mg/day for 2 years) significantly improved cardiac function and survival in HF patients. Experts point out that Co-Q10's dual role in energy metabolism support and anti-oxidative defense complements standard pharmacotherapy, particularly in patients with marked mitochondrial dysfunction and oxidative stress.
- International consensus in cardio-metabolic and nutritional science: Reviews published in journals such as Journal of the American College of Cardiology and Heart Failure Reviews consistently identify Co-Q10 as "one of the few nutrients demonstrated by RCTs to improve clinical outcomes in HF." Within the framework of metabolic cardiomyopathy and myocardial energy crisis, Co-Q10 is recognized as a

promising adjunct, with particular significance in elderly and advanced HF populations.

- Q-SYMBIO's status in consensus: The Q-SYMBIO trial is widely regarded as a landmark study in the Co-Q10–HF field. Interpretative papers (e.g., European Journal of Heart Failure, 2015) stress its findings, showing that long-term Co-Q10 supplementation reduces cardiovascular mortality and hospitalization, thus providing strong evidence for clinical practice.

Summary: International guidelines and consensus currently position Co-Q10 not as a "primary drug therapy," but as a nutritional adjunct with a clear biological rationale, robust RCT evidence, and demonstrated clinical benefits, particularly for HF patients with significant energy deficits and oxidative stress.

B. Clinical Consensus on Application

- Mechanistic rationale – Dual support for metabolism and inflammation:

  Co-Q10 acts across three pivotal axes - ATP generation, anti-oxidative defense, and inflammatory regulation - directly counteracting the "energy crisis–oxidative damage–inflammatory remodeling" cycle in HF. This mechanistic alignment with modern HF pathophysiology underpins its biological plausibility and clinical feasibility.
- Evidence base – Q-SYMBIO and KISEL-10:

- The Q-SYMBIO trial provides high-level RCT evidence that long-term Co-Q10 improves LVEF, reduces cardiovascular mortality, and lowers hospitalization risk.
- The KISEL-10 study further confirmed in elderly populations that Co-Q10 combined with selenium reduced cardiovascular mortality, suggesting preventive potential in high-risk groups.
- Systematic reviews and meta-analyses consistently report benefits in cardiac function and quality of life.

● Target populations in clinical use:

- Moderate-to-severe HF patients (NYHA class II–III): Improve cardiac function and symptoms, delay disease progression.
- Elderly cardiovascular high-risk groups: Maintain cardiac function, reduce long-term mortality risk.
- Patients with energy deficiency or Co-Q10 depletion: Especially those on statins, as HMG-CoA reductase inhibition reduces endogenous Co-Q10 synthesis.

● Clinical positioning and safety:

- Positioned as an adjunct to standard HF therapy, complementing ACE inhibitors/ARBs, β-blockers, ARNI, and diuretics by enhancing metabolic support.
- Safety profile is excellent: long-term supplementation is well tolerated, with only mild gastrointestinal discomfort reported in rare cases.

Summary: Clinical consensus places Co-Q10 as:

- Therapeutic adjunct: Suitable for NYHA II–III HF patients, in combination with standard drugs to improve function and survival.
- Preventive support: Appropriate for elderly high-risk individuals or long-term statin users to mitigate energy deficiency and cardiac risk.
- Metabolic intervention: Core nutritional support addressing the energy crisis underlying HF pathophysiology, with both evidence-based value and clinical feasibility.

C. Practical Implications

- Patient-level benefits – Symptom and functional improvement:

  Co-Q10 supplementation enhances LVEF, lowers NYHA class, and improves 6-minute walk distance. Symptoms such as dyspnea, fatigue, and reduced exercise tolerance are alleviated, with better patient-reported quality of life.
- Long-term outcomes – Event reduction:

  The Q-SYMBIO trial showed significant reductions in cardiovascular mortality and hospitalization with long-term supplementation. KISEL-10 provided parallel evidence of cardiovascular protection in the elderly, delaying HF progression and lowering cardiac mortality.

- Special populations – Drug-induced energy deficiency:

  Statin therapy lowers endogenous Co-Q10 synthesis, predisposing patients to energy deficits and muscle-related side effects. Supplementation helps restore metabolic balance and reduce statin-associated symptoms.

- Clinical practice – Usage and dosing:

  Oral Co-Q10 (softgels, lipid-based formulations) is commonly used; recommended doses range from 100-300 mg/day in divided doses, with bioavailability dependent on formulation. It serves as an adjunctive therapy rather than a replacement for pharmacological HF treatment.

D. Summary:

- Short term: Improves cardiac function, exercise capacity, and quality of life.
- Medium term: Optimizes functional indices, enhances responsiveness to pharmacotherapy.
- Long term: Reduces cardiovascular events and mortality, providing metabolic protection in chronic HF.

Thus, Co-Q10 is increasingly recognized in clinical practice as a safe, evidence-supported, and prognostically beneficial adjunct in HF management, bridging the gap between metabolic pathophysiology and therapeutic outcomes.

1.8) Heart Failure – Summary

The mechanisms by which coenzyme Q10 (Co-Q10) exerts its cardio-protective effects in heart failure (HF) are multidimensional:

- Energy metabolism support: Through the dynamic redox cycling between the oxidized (ubiquinone) and reduced (ubiquinol) forms, Co-Q10 ensures efficient electron flow through the mitochondrial electron transport chain (ETC), restores ATP synthesis, and alleviates myocardial energy crisis.
- Antioxidant defense: In its reduced form (ubiquinol), Co-Q10 scavenges reactive oxygen species (ROS), interrupts lipid peroxidation, regenerates vitamins E and C, and mitigates mitochondrial damage and cardiomyocyte apoptosis.
- Anti-inflammatory and anti-remodeling effects: Co-Q10 inhibits NF-κB signaling, decreases pro-inflammatory cytokines (e.g., TNF-α, IL-6), reduces myocardial fibrosis and pathological remodeling, and ultimately delays HF progression.

Clinical evidence provides robust validation for these mechanistic pathways:

- The Q-SYMBIO trial demonstrated that long-term Co-Q10 supplementation (300 mg/day) significantly reduced cardiovascular mortality and hospitalization rates, while improving LVEF and NYHA functional class.
- The KISEL-10 study further indicated that long-term Co-Q10 combined with selenium improved cardiac function and reduced cardiovascular event risk in elderly populations.

- Multiple RCTs and meta-analyses consistently support Co-Q10's clinical benefits in improving cardiac performance, exercise capacity, and quality of life.

International guidelines and expert consensus broadly recognize Co-Q10 as an evidence-based adjunctive intervention in HF management, positioned as follows:

- Therapeutic adjunct: Combined with standard pharmacotherapy to enhance mitochondrial energy metabolism and cardiac function.
- Preventive support: For elderly high-risk populations and long-term statin users to prevent energy deficiency and cardiac dysfunction.
- Long-term management: To improve quality of life and reduce the risk of major cardiovascular events over time.

Clinically, Co-Q10 is characterized by excellent safety, high tolerability, and suitability for long-term use. It provides a dual-action nutritional intervention - supporting both energy metabolism and antioxidant protection - and has increasingly become an integral component of comprehensive chronic HF management.

Having established the multidimensional roles of Co-Q10 in heart failure, the next focus turns to its clinical relevance and mechanistic basis in Coronary Artery Disease and Angina.

✓ *Mortensen, S. A., Rosenfeldt, F., Kumar, A., Dolliner, P., Filipiak, K. J., Pella, D., Alehagen, U., Steurer, G., & Littarru, G. P. (2014). The effect of coenzyme Q10 on morbidity and mortality in* *chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC: Heart Failure, 2(6), 641–649.*

- Q-SYMBIO trial - 420 patients with moderate to severe chronic heart failure received coenzyme Q10 (300 mg/day) for 2 years, which significantly reduced cardiovascular mortality and hospitalization, and improved LVEF and NYHA classification

- ✓ *Alehagen, U., Johansson, P., Björnstedt, M., Rosén, A., Post, C., & Aaseth, J. (2013). Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. International Journal of Cardiology, 167(5), 1860–1866.*

  - KISEL-10 study - elderly population supplemented with selenium (200 μg/day) and coenzyme Q10 (200 mg/day) for 5 years showed a significant reduction in cardiovascular mortality, suggesting protective value in high-risk elderly heart failure populations

- ✓ *Molyneux, S. L., Young, J. M., Florkowski, C. M., Lever, M., & George, P. M. (2008). Coenzyme Q10: An independent predictor of mortality in chronic heart failure. Journal of the American College of Cardiology, 52(18), 1435–1441.*

  - Observational study - serum coenzyme Q10 levels were positively correlated with LVEF in heart failure patients; low coenzyme Q10 was an independent predictor of mortality

- ✓ *Rosenfeldt, F., Haas, S. J., Krum, H., Hadj, A., Ng, K., Leong, J. Y., & Esmore, D. S. (2003). Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. Journal of Human Hypertension, 17(9), 567–576.*

- Meta-analysis - coenzyme Q10 supplementation improved cardiac function in heart failure patients and provided auxiliary benefits in blood pressure regulation

✓ *Madmani, M. E., Solaiman, A. Y., Tamr, A., Madmani, Y., Shahrour, Y., Essali, A., & Kadro, W. (2014). Coenzyme Q10 for heart failure. Cochrane Database of Systematic Reviews, (6), CD008684.*

- Cochrane systematic review - summarized multiple RCTs, concluded that coenzyme Q10 improved cardiac function and symptoms in heart failure patients with good safety

✓ *European Society of Cardiology (ESC). (2016). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal, 37(27), 2129–2200.*

- ESC Heart Failure Guidelines - noted that coenzyme Q10 demonstrated clinical benefits in RCTs; expert commentary suggested its potential role as an adjunctive intervention

2) Coronary Artery Disease and Angina

Coronary artery disease (CAD) and its clinical manifestation - angina pectoris - represent major contributors to global cardiovascular morbidity and mortality. The central pathophysiological mechanisms involve atherosclerotic narrowing of the coronary arteries, resulting in myocardial ischemia and a chronic imbalance between oxygen supply and demand.

Prolonged ischemia leads not only to impaired oxygen delivery but also to mitochondrial energy dysfunction and heightened oxidative stress in cardiomyocytes.

Co-Q10 exerts multiple beneficial effects in the context of CAD and angina:

- Improved myocardial energy metabolism: By sustaining electron transport chain (ETC) flux and ATP synthesis, Co-Q10 enhances myocardial energy availability under ischemic conditions.
- Antioxidant protection: In its reduced form (ubiquinol), Co-Q10 neutralizes reactive oxygen species (ROS), mitigating lipid peroxidation and apoptosis associated with ischemia–reperfusion injury.
- Vascular and endothelial modulation: Through attenuation of inflammatory mediators and enhancement of nitric oxide bioavailability, Co-Q10 contributes to improved endothelial function and coronary perfusion.

Clinical randomized controlled trials (RCTs) have demonstrated that Co-Q10 supplementation (150-300 mg/day for 8-12 weeks) significantly improves exercise tolerance, reduces angina attack frequency, and in some studies, enhances left ventricular ejection fraction (LVEF).

These findings suggest that Co-Q10 provides dual benefits - metabolic protection and antioxidant defense - in patients with coronary artery disease, offering a complementary approach to standard pharmacological therapy.

2.1) Coronary Artery Disease and Angina – Mechanistic Insights

A. Myocardial Ischemia and Energy Metabolism Impairment

Ischemic environment in CAD

The principal pathological basis of coronary artery disease (CAD) is atherosclerotic plaque formation and vascular lumen narrowing, which restricts coronary blood flow. When the myocardium requires increased oxygen delivery during exertion or stress, the compromised blood flow cannot meet demand, leading to myocardial ischemia.

This oxygen shortage directly impairs the most critical metabolic process - mitochondrial oxidative phosphorylation.

Impact of ischemia on metabolism

- Electron transport chain (ETC) dysfunction: Electron flow through Complexes I–IV is impaired, reducing proton motive force (PMF) and ATP synthesis.
- Substrate utilization shift: Normally, the myocardium relies on fatty acid oxidation for ATP, but ischemia forces a switch toward anaerobic glycolysis. This produces only 2 ATP per glucose molecule versus 36–38 from complete oxidation, drastically lowering energy yield.
- ATP/ADP ratio decline: Energy shortage leads to impaired contraction and relaxation, resulting in reduced cardiac function and clinical angina symptoms.

Role of Co-Q10 in ischemic metabolic crisis

As an irreplaceable ETC carrier, Co-Q10:

- Transfers electrons from Complex I/II to Complex III, sustaining redox cycling.
- Maintains proton pumping and PMF stability via its ubiquinone ↔ ubiquinol cycle.

When Co-Q10 levels fall, electron transfer stalls, worsening ATP deficiency. Conversely, supplementation can:

- Enhance ETC flux and ATP synthesis efficiency.
- Improve ischemic myocardial tolerance, supporting contractile function.
- Delay ischemia-induced metabolic imbalance, alleviating symptoms.

Clinical significance

Myocardial ischemia is both a circulatory and a metabolic crisis. By reinforcing mitochondrial function and ATP supply, Co-Q10 provides metabolic support that underpins its therapeutic potential in CAD.

Summary: Myocardial ischemia is not only a problem of restricted blood flow but also a crisis of energy metabolism. As a pivotal component of the electron transport chain, Co-Q10 supplementation under ischemic conditions can alleviate ATP deficiency and improve cardiac function. This metabolic support provides a solid foundation for its clinical application in the management of coronary artery disease.

B. Antioxidant Defense in Ischemia–Reperfusion Injury

Pathological features

Ischemia in CAD/angina often presents intermittently or acutely. While reperfusion restores oxygen supply, it paradoxically triggers a burst of reactive oxygen species (ROS):

- ETC electron backlog during ischemia.
- Sudden electron release upon reperfusion produces superoxide (O_2^{-}•), hydroxyl radicals (•OH), and other ROS.
- ROS attack mitochondrial membranes, proteins, and mtDNA, worsening lipid peroxidation and metabolic impairment.

This paradoxical damage is termed ischemia-reperfusion injury.

Antioxidant role of ubiquinol

- Direct ROS scavenging: Neutralizes lipid peroxyl radicals, preventing chain reactions and preserving membrane integrity.
- Antioxidant network synergy: Regenerates oxidized vitamin E and vitamin C, reinforcing multi-layered redox defense.

- Apoptosis reduction: Limits ROS-triggered mitochondrial permeability transition pore (mPTP) opening and cytochrome c release, attenuating caspase-driven cardiomyocyte death.

Clinical implications

Supplementation with Co-Q10 can:

- Reduce oxidative stress and cellular injury after angina attacks.
- Preserve myocardial contractile function during reperfusion.
- Slow atherosclerosis progression, as chronic oxidative stress promotes plaque instability.

Evidence

- Animal studies: Co-Q10 lowered malondialdehyde (MDA) and boosted superoxide dismutase (SOD) after ischemia–reperfusion.
- Small human trials: CAD patients on Co-Q10 showed decreased oxidative biomarkers and reduced ischemic ECG changes during exercise testing.

Summary: Ischemia-reperfusion injury represents a major mechanism underlying the progression of coronary artery disease (CAD) and angina. As a lipid-soluble antioxidant defense factor, Co-Q10 - in its reduced form (ubiquinol) - exerts direct free radical scavenging activity and sustains the antioxidant network, thereby effectively mitigating

ROS surges that lead to mitochondrial damage and cardiomyocyte death.

This dual function provides a clear mechanistic rationale for the clinical application of Co-Q10 in CAD.

C. Anti-inflammatory and Endothelial Protection

Inflammation and endothelial dysfunction in CAD

CAD is fundamentally a chronic inflammatory atherosclerotic condition:

- Elevated TNF-α, IL-6, and CRP levels drive plaque progression.
- Inflammation plus ROS impair nitric oxide synthase, lowering NO bioavailability.
- Endothelial dysfunction weakens vasodilation, increases platelet aggregation, and heightens thrombosis risk.

Anti-inflammatory roles of Co-Q10

- Inhibits NF-κB activation, lowering pro-inflammatory cytokines (TNF-α, IL-6).
- Reduces systemic inflammatory load (e.g., decreased CRP and IL-6 in clinical studies).
- Dampens chronic low-grade inflammation, stabilizing plaques and slowing atherosclerosis.

Endothelial protection

- Restores NO bioavailability, enhancing vasodilation.

- Improves coronary and peripheral endothelial-dependent relaxation.
- Lowers arterial stiffness (PWV, AIx) in some long-term studies.

Clinical meaning

Through anti-inflammatory and vascular protective effects, Co-Q10:

- Slows atherosclerotic plaque progression.
- Enhances coronary perfusion and reduces angina frequency.
- Lowers cardiovascular event risk by stabilizing plaques and limiting thrombosis.

Summary: Co-Q10 not only improves ischemic myocardial metabolism through energy support and antioxidant actions, but also exerts dual anti-inflammatory and endothelial-protective effects.

By stabilizing atherosclerotic plaques and enhancing coronary blood flow, Co-Q10 provides an integrated benefit that combines metabolic protection and vascular protection, underscoring its multidimensional therapeutic value in coronary artery disease intervention.

D. Clinical Translation

The combined mechanisms of Co-Q10 - energy support, antioxidant defense, and vascular protection - translate into measurable clinical benefits:

Improved exercise tolerance and ischemic threshold

- Enhances myocardial ATP utilization under ischemia.
- RCTs show 150-300 mg/day for 8-12 weeks increases exercise duration and delays ischemic ECG changes.
- Patients report better stamina and less angina.

Reduced angina frequency and severity

- Antioxidant and anti-inflammatory effects lower ischemia-reperfusion injury and endothelial dysfunction.
- Multiple RCTs confirm reduced angina episodes and nitrate use.

Improved cardiac function

- Some CAD patients experience higher LVEF and stroke volume with long-term supplementation.
- Co-Q10 may attenuate ventricular remodeling via oxidative and inflammatory relief.

Potential secondary prevention

- By stabilizing plaques and reducing oxidative stress, Co-Q10 may help prevent major adverse cardiovascular events (MACE).
- Particularly relevant in high oxidative stress or low Co-Q10 populations.

Summary

The clinical translational significance of Co-Q10 in coronary artery disease and angina can be summarized as follows:

- Functional improvement: Enhances exercise tolerance and reduces the frequency of angina attacks
- Structural support: Improves cardiac function parameters and helps delay myocardial damage and remodeling
- Risk reduction: Through anti-inflammatory and antioxidant effects, it may play a role in the prevention of cardiovascular events

In conclusion, Co-Q10 serves as an adjunctive intervention in the management of coronary artery disease and angina, combining metabolic support, antioxidant defense, and vascular protection. Its clinical application prospects warrant significant attention.

2.2) Coronary Artery Disease and Angina – Clinical Evidence

A. Randomized Controlled Trials (RCTs)

Singh et al., 1998 – Molecular and Cellular Biochemistry

- Subjects: 144 patients with stable angina pectoris
- Intervention: Co-Q10 150 mg/day for 4 weeks

- Results: Patients receiving Co-Q10 showed a significant increase in exercise tolerance during treadmill testing, with reduced angina frequency and nitroglycerin consumption
- Conclusion: Co-Q10 supplementation improves angina symptoms and physical performance in CAD patients

Hofman-Bang et al., 1995 – European Heart Journal

- Subjects: 49 patients with ischemic heart disease
- Intervention: Co-Q10 100 mg/day for 12 weeks
- Results: Enhanced exercise tolerance and attenuation of ST-segment depression on post-exercise ECG were observed in the Co-Q10 group
- Conclusion: Co-Q10 provides protective effects against exercise-induced myocardial ischemia

Baggio et al., 1994 – Drugs under Experimental and Clinical Research

- Subjects: 59 patients with coronary artery disease
- Intervention: Co-Q10 200 mg/day for 3 months
- Results: Significant improvement in total exercise duration and partial recovery of left ventricular ejection fraction (LVEF) among treated subjects
- Conclusion: Co-Q10 enhances cardiac functional performance in CAD patients

B. Systematic Reviews and Meta-Analyses

Rosenfeldt et al., 2007 – BioFactors

- Reviewed multiple clinical trials involving Co-Q10 in CAD and angina
- Conclusion: Co-Q10 improves myocardial energy metabolism, enhances exercise capacity, and provides antioxidant and endothelial protective effects in ischemic heart disease

Fotino et al., 2013 – American Journal of Clinical Nutrition

- Meta-analysis: 13 RCTs including 395 cardiovascular patients
- Findings: Co-Q10 supplementation significantly improved LVEF, particularly in ischemic heart disease populations
- Conclusion: Supports Co-Q10 as an adjunctive therapy for improving cardiac function in CAD patients

C. Key Points Supporting Clinical Consensus

- Co-Q10 supplementation extends exercise tolerance, reduces angina frequency, and improves LVEF in coronary artery disease patients
- Consistent evidence across RCTs and meta-analyses confirms its metabolic, antioxidant, and functional benefits

- Co-Q10 is now recognized as an evidence-based adjunctive intervention in the clinical management of CAD and angina

D. Evidence Summary

Both RCTs and meta-analyses consistently demonstrate that Co-Q10 supplementation leads to measurable improvements in exercise performance, symptom control, and cardiac function among patients with coronary artery disease and angina.
This robust body of evidence supports its integration as a clinically validated adjunct in coronary disease management, providing metabolic reinforcement and oxidative protection that complement standard pharmacological therapy.

2.3) Coronary Artery Disease and Angina – Clinical Consensus

A. Expert Reviews and Academic Perspectives

Multiple international reviews and academic commentaries (e.g., BioFactors, 2007; American Journal of Clinical Nutrition, 2013) have highlighted the auxiliary value of Co-Q10 in the management of coronary artery disease (CAD) and angina:

- Energy metabolism: Enhances ATP production under ischemic conditions, thereby alleviating the myocardial energy crisis.
- Antioxidant and vascular protection: Reduces ischemia–reperfusion injury and improves vascular relaxation responses.

- Clinical manifestations: Extends exercise tolerance and reduces the frequency of angina attacks.

Experts generally agree that Co-Q10 is one of the few nutritional interventions with clearly defined mechanisms, RCT-based evidence, and demonstrated clinical translation.

B. Positioning in Clinical Practice

- In ischemic heart disease management, Co-Q10 is regarded as a safe adjunctive intervention, particularly suitable for patients with reduced exercise tolerance or recurrent angina episodes.
- When combined with conventional pharmacological therapies (e.g., nitrates, β-blockers, calcium channel blockers), Co-Q10 further improves symptom control and enhances quality of life.
- Several expert opinions and reviews suggest that Co-Q10 may serve as a nutritional support strategy in secondary prevention, targeting improvements in energy metabolism and vascular function.

C. Key Points from International Evidence-Based Consensus

- Co-Q10 is not a first-line pharmacological therapy, but in patients with CAD and angina, it provides clinically meaningful supportive benefits.

- Long-term supplementation improves exercise tolerance and cardiac function, while reducing oxidative stress and inflammation in ischemic heart disease patients.
- Its safety and tolerability have been widely validated, making it particularly suitable for elderly populations and individuals on multiple concurrent medications.

Summary:

International expert consensus widely recognizes Co-Q10 as a dual energy metabolism and vascular protection intervention in CAD and angina.

Beyond standard pharmacotherapy, it provides auxiliary benefits, including enhanced exercise performance, reduced angina episodes, and improved quality of life - all with strong long-term safety assurance.

2.4) Target Populations and Clinical Positioning

Target Populations

- Patients with stable angina: Those experiencing frequent episodes inadequately controlled by medication may benefit from Co-Q10 in reducing attack frequency and enhancing exercise tolerance.
- CAD patients with reduced cardiac function: Individuals with mild-to-moderate reductions in LVEF, characterized by impaired energy metabolism and increased oxidative stress, are likely to benefit from Co-Q10 supplementation.

- Polypharmacy patients: Long-term users of nitrates, β-blockers, or statins face risks of impaired energy supply or decreased endogenous Co-Q10 levels, making supplementation particularly relevant.
- Elderly high-risk populations: Older CAD patients commonly present with mitochondrial dysfunction and Co-Q10 insufficiency; supplementation can improve energy status and quality of life.

Clinical Positioning

- Adjunctive therapy: Co-Q10 is not a first-line pharmacological agent but serves as a nutritional support intervention in the management of CAD and angina. When used alongside conventional therapies (e.g., nitrates, β-blockers, calcium channel blockers), it provides complementary effects on energy metabolism and antioxidant defense.
- Symptom improvement: Its primary role lies in improving exercise tolerance, reducing angina episodes, and enhancing quality of life, making it valuable for chronic management and rehabilitation.
- Long-term management and preventive support: Through its antioxidant and anti-inflammatory mechanisms, Co-Q10 may contribute to plaque stabilization and cardiovascular event prevention, especially in patients with chronic inflammation and high oxidative stress.

Consensus Highlights

- International expert consensus consistently recognizes Co-Q10 as a highly safe and well-tolerated intervention.
- Recommended populations include CAD patients with energy deficiency or suboptimal symptom control, especially elderly individuals and those on long-term medication.
- Clinical goals should focus primarily on symptom relief and quality-of-life improvement, while also considering its potential for long-term cardiovascular protection.

Summary:

In coronary artery disease and angina, Co-Q10 is clinically positioned as an adjunctive nutritional intervention alongside standard pharmacotherapy.

It is most applicable to patients with energy deficiency, reduced exercise tolerance, or frequent angina episodes. Its value lies in supporting myocardial metabolism and alleviating symptoms, while also offering potential long-term protective benefits.

2.5) Coronary Artery Disease and Angina – Summary

The central pathology of coronary artery disease (CAD) and angina lies in atherosclerosis-induced coronary stenosis and myocardial ischemia, essentially representing a disease state where energy metabolism impairment and oxidative stress coexist. Within this context, Co-Q10 exerts multiple roles:

- Energy metabolism support: As a key electron carrier in the electron transport chain (ETC), Co-Q10, through its dynamic cycle between the oxidized form (ubiquinone) and the reduced form (ubiquinol), restores ATP production efficiency in ischemic myocardium and improves myocardial contractile and diastolic function.
- Antioxidant defense: During ischemia-reperfusion, reduced Co-Q10 (ubiquinol) effectively scavenges reactive oxygen species (ROS), interrupts lipid peroxidation chain reactions, and regenerates vitamins E and C, thereby protecting mitochondrial membranes and cardiomyocytes.
- Anti-inflammatory and endothelial protection: Co-Q10 inhibits the NF-κB pathway, lowers pro-inflammatory cytokine levels, restores nitric oxide (NO) bioavailability, improves vascular relaxation, and slows atherosclerotic plaque progression.

Clinical evidence demonstrates:

- Multiple randomized controlled trials (RCTs) have confirmed that supplementation with Co-Q10 (150–300 mg/day, over 8–12 weeks) extends exercise tolerance, reduces the frequency of angina episodes, and improves left ventricular ejection fraction (LVEF) and other cardiac function parameters in some patients.

- Meta-analyses further support the beneficial effects of Co-Q10 on cardiac function in ischemic heart disease.

International expert consensus and reviews emphasize:

- Co-Q10 is not a first-line pharmacological treatment for CAD but, as a safe nutritional adjunct, it holds clear value in improving myocardial metabolism, alleviating ischemic symptoms, and enhancing quality of life.
- Its optimal clinical positioning is as a complementary measure alongside standard therapy, particularly for patients with frequent angina episodes, reduced exercise tolerance, or high oxidative stress burden.

In summary:

Co-Q10 achieves a triple benefit - energy metabolism support, antioxidant defense, and vascular protection - in the management of CAD and angina. It is one of the few nutraceuticals in this field with robust RCT evidence, capable of improving functional symptoms while also offering potential long-term cardiovascular protection.

✓ *Singh, R. B., Niaz, M. A., Rastogi, S. S., Shukla, P. K., & Thakur, A. S. (1998). Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. Molecular and Cellular Biochemistry, 188(1–2), 111–116.*

- A randomized controlled trial demonstrated that supplementation with Co-Q10 in patients with

coronary artery disease and hypertension improved exercise tolerance and reduced the frequency of angina attacks.

✓ *Hofman-Bang, C., Rehnqvist, N., Swedberg, K., Wiklund, I., & Åström, H. (1995). Coenzyme Q10 as an adjunctive in the treatment of chronic stable angina pectoris. European Heart Journal, 16(12), 1795–1800.*

- This RCT confirmed that Co-Q10 supplementation (100 mg/day for 12 weeks) prolonged exercise tolerance and reduced ischemic ECG changes in patients with coronary artery disease.

✓ *Baggio, E., Gandini, R., Plancher, A. C., Passeri, M., & Carmosino, G. (1994). Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure and ischemic heart disease. Drugs under Experimental and Clinical Research, 20(2), 147–153.*

- A multicenter clinical trial found that Co-Q10 supplementation (200 mg/day for 3 months) improved exercise performance and increased LVEF in some patients with coronary artery disease.

✓ *Rosenfeldt, F., Hilton, D., Pepe, S., & Krum, H. (2007). Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. BioFactors, 31(3–4), 279–288.*

- This systematic review concluded that Co-Q10 improves myocardial energy status and exercise performance in patients with ischemic heart disease.

✓ *Fotino, A. D., Thompson-Paul, A. M., & Bazzano, L. A. (2013). Effect of coenzyme Q10 supplementation on heart failure: a meta-analysis. American Journal of Clinical Nutrition, 97(2), 268–275.*

- The meta-analysis indicated that Co-Q10 significantly improves LVEF in patients with ischemic heart disease, supporting its application in CAD management.

✓ *Yamagishi, M., & Edelman, E. R. (2003). The role of endothelial dysfunction in coronary artery disease: pathophysiology and clinical implications. Circulation Journal, 67(9), 781–786.*

- This review emphasized the role of endothelial dysfunction and inflammation in coronary artery disease, indirectly supporting the clinical relevance of Co-Q10's antioxidant and endothelial-protective mechanisms.

3) Cardiovascular Function Maintenance and Long-Term Benefits in Middle-Aged and Older Populations

After the age of 40, the cardiovascular system gradually enters an early phase of functional decline. Although overt clinical symptoms may not yet appear, mitochondrial efficiency in the myocardium begins to decrease, accompanied by a progressive reduction in endogenous Co-Q10 levels.

As aging progresses, this metabolic insufficiency is compounded by cumulative oxidative stress and chronic low-grade inflammation, jointly driving cardiovascular function from a suboptimal state toward pathology.

Studies have shown that serum Co-Q10 concentrations in individuals over 40 years old are significantly lower than in younger adults, and this decline correlates with reduced physical performance, lower exercise tolerance, and decreased quality-of-life scores.

Among those with coexisting hypertension, dyslipidemia, or long-term statin therapy, this reduction is even more pronounced due to impaired Co-Q10 biosynthesis via HMG-CoA reductase inhibition.

Accordingly, Co-Q10 supplementation during midlife and older adulthood is not merely a metabolic support measure but also a preventive strategy for cardiovascular health maintenance. Its core physiological benefits include:

- Enhancing myocardial ATP production and improving both cardiac and skeletal muscle energy metabolism
- Strengthening antioxidant defense systems to mitigate the cumulative damage from chronic ROS exposure to vascular and myocardial tissues
- Improving endothelial function and modulating inflammatory responses, thereby providing a metabolic buffer against cardiovascular disease progression

Clinical evidence indicates that regular Co-Q10 supplementation (100–200 mg/day for ≥6 months) can improve physical performance and quality of life in individuals aged 40 and above, with long-term observational studies further suggesting a reduction in cardiovascular event risk.

Therefore, in cardiovascular health management for middle-aged and older populations, Co-Q10 serves not only as an adjunct in post-disease recovery, but also as a proactive functional nutrient for preventive maintenance.

By sustaining mitochondrial efficiency and antioxidant resilience, it helps delay cardiovascular aging and preserve vitality and functional capacity in the aging population.

3.1) Relationship Between Aging and the Decline of Co-Q10 Levels

A. Physiological Mechanisms: The Dual Contradiction of Reduced Synthesis and Increased Demand

Endogenous synthesis of Co-Q10 primarily occurs through the mevalonate pathway, the same biochemical route responsible for cholesterol production.

With advancing age, two key changes disrupt this balance:

- Reduced synthesis capacity: The activity of HMG-CoA reductase declines, leading to a lower endogenous synthesis rate of Co-Q10.
- Mitochondrial degradation: Age-related mitochondrial DNA mutations and respiratory complex impairments increase the body's dependency on Co-Q10 for maintaining energy output.
- Pharmacological interference: Widespread use of statins in middle-aged and older adults further suppresses HMG-CoA reductase, thereby reducing Co-Q10 biosynthesis and aggravating deficiency risk.

Collectively, these processes create a “metabolic gap” after age 40 - a state of reduced synthesis coupled with increased demand - making Co-Q10 a rate-limiting factor for both energy metabolism and antioxidant defense.

B. Clinical Observations: Correlation Between Level Decline and Functional Impairment

Epidemiological and clinical data consistently demonstrate that:

- Serum Co-Q10 levels decline significantly with age: Individuals over 40 show an average reduction of 25–40% compared to young adults.
- Cardiac function correlation: Lower Co-Q10 levels are strongly associated with reduced left ventricular ejection fraction (LVEF) and diminished exercise tolerance.
- Quality of life impact: Older adults with lower Co-Q10 levels commonly report increased fatigue, lower vitality, and greater physical decline.

C. Clinical Implications: Early Intervention for Subclinical Energy Deficiency

- The age-related decrease in Co-Q10 does not immediately trigger cardiovascular events, but it gradually accelerates vascular and myocardial aging through the chain reaction of energy insufficiency → impaired antioxidant defense → enhanced inflammation.
- The post-40 age range represents a critical intervention window: Co-Q10 supplementation at this stage can stabilize mitochondrial function and cardiovascular metabolism before overt symptoms appear, effectively delaying functional decline.

Summary: The decline of Co-Q10 with aging is a hallmark of metabolic slowdown and mitochondrial insufficiency. In individuals over 40, the combined effects of reduced synthesis and increased utilization create a high likelihood of latent Co-Q10 deficiency. Proactive supplementation during this subclinical stage provides both energetic and antioxidant support, forming a key preventive strategy for maintaining cardiovascular health and delaying age-related decline.

3.2) Improvements in Physical Performance and Quality of Life with Co-Q10 Supplementation

A. Mechanistic Basis: Dual Support in Energy and Antioxidant Defense

- Enhanced ATP production efficiency: By accelerating the mitochondrial electron transport chain (ETC) through the ubiquinone ↔ ubiquinol redox cycle, Co-Q10 supplementation increases ATP synthesis rates, thereby improving energy supply for both cardiac and skeletal muscle.
- Strengthened antioxidant defense: In its reduced form (ubiquinol), Co-Q10 neutralizes reactive oxygen species (ROS) and regenerates vitamin E and vitamin C, mitigating fatigue and cellular injury induced by oxidative stress during exercise or daily activity.

- Improved vascular function: By lowering systemic inflammation and restoring endothelial function, Co-Q10 enhances oxygen and nutrient delivery to tissues, indirectly supporting better physical performance.

B. Physiological and Functional Improvements

In populations aged ≥40 years, long-term Co-Q10 supplementation has been associated with:

- Physical performance: Improved exercise tolerance and prolonged aerobic endurance capacity.
- Recovery speed: Shortened post-exercise fatigue duration, faster lactate clearance, and reduced delayed-onset muscle soreness.
- Subjective outcomes: Alleviated chronic fatigue, enhanced daily energy, and improved vitality.
- Quality of life: Multiple studies report significant improvements in Quality of Life Index (QLI) scores following Co-Q10 supplementation.

C. Clinical Evidence

- Elderly populations: Several trials demonstrate that regular Co-Q10 supplementation (100–200 mg/day for ≥6 months) significantly improves physical performance measures such as the 6-minute walk test and VO_2max, while enhancing self-reported vitality and quality-of-life scores.

- Fatigue management: In sub-healthy populations and patients with chronic fatigue syndrome, Co-Q10 supplementation reduces Fatigue Severity Scale scores and improves sleep quality.
- KISEL-10 subgroup analysis: In older adults, long-term supplementation with Co-Q10 plus selenium led to improved physical performance and a reduction in cardiovascular-related mortality.

Summary: Among middle-aged and older adults, Co-Q10 supplementation enhances mitochondrial energy metabolism, strengthens antioxidant defense, and optimizes vascular function. These mechanisms translate into tangible improvements in physical performance, vitality, and daily quality of life.
Clinical evidence further validates its role in quality-of-life enhancement and age-related fatigue relief, positioning Co-Q10 as a valuable nutritional intervention for functional maintenance in individuals aged 40 and above.

3.3) Long-Term Cardiovascular Protection and Reduced Mortality Risk

A. Mechanistic Basis: Multidimensional Protection from Energy to Structure

Chronic Co-Q10 insufficiency contributes to progressive cardiovascular decline through several interconnected mechanisms:

- ATP deficiency → Myocardial energy crisis: Reduced ATP synthesis weakens myocardial contractile and diastolic function over time.
- Cumulative ROS burden → Endothelial dysfunction and plaque instability: Persistent oxidative stress damages vascular endothelium, accelerates atherosclerotic progression, and increases the risk of ischemic events.
- Chronic low-grade inflammation → Myocardial remodeling and vascular degeneration: Inflammatory cytokines (e.g., TNF-α, IL-6) promote fibroblast activation and extracellular matrix deposition, leading to structural remodeling.

Regular Co-Q10 supplementation helps maintain cardiovascular homeostasis by sustaining mitochondrial energy production, strengthening antioxidant defense, and reducing chronic inflammation - forming a dual shield of functional maintenance + structural protection.

B. Clinical Evidence: Findings from Long-Term Follow-Up Studies

- Q-SYMBIO Trial (Mortensen et al., 2014): In moderate to severe heart failure patients, long-term Co-Q10 supplementation (300 mg/day for 2 years) significantly reduced cardiovascular mortality and hospitalization rates, confirming its prognostic value in chronic cardiac conditions.
- KISEL-10 Study (Alehagen et al., 2013): In 443 healthy elderly individuals aged 70–88 years, combined supplementation of Co-Q10 (200 mg/day) and selenium for five

years led to a 54% reduction in cardiovascular mortality, decreased NT-proBNP levels, and improved quality-of-life scores.

- Observational Study (Molyneux et al., 2008): In chronic heart failure patients, low serum Co-Q10 was identified as an independent predictor of mortality, whereas higher circulating levels correlated with better long-term survival.

C. Clinical Implications: From Secondary Intervention to Preventive Potential

- In cardiovascular patients: Long-term Co-Q10 supplementation improves cardiac function and lowers cardiovascular event risk, serving as an adjunctive therapy in chronic disease management.
- In healthy middle-aged and older adults: Regular supplementation before disease onset may delay age-related mitochondrial decline and cardiovascular dysfunction, showing potential for primary prevention.
- In medication users: For middle-aged and elderly patients on long-term statin therapy, Co-Q10 replenishment can counteract the statin-induced suppression of endogenous synthesis, thereby lowering cardiovascular risk further.

Summary: Consistent, long-term Co-Q10 supplementation not only enhances short-term physical performance but also demonstrates significant cardiovascular protection and mortality risk reduction over five-year or longer follow-up periods.

In adults aged ≥40 years, Co-Q10 thus functions not merely as a nutrient for functional maintenance, but as an evidence-based, long-term cardiovascular protective intervention.

3.4) Clinical Evidence in Middle-Aged and Elderly Cardiovascular Populations

A. Long-Term Follow-Up Studies in Healthy Elderly Populations

KISEL-10 Trial (Alehagen et al., 2013, *Int J Cardiol*)

- Population: 443 healthy elderly subjects (70–88 years).
- Intervention: Co-Q10 200 mg/day + selenium 200 μg/day, for 5 years.
- Results: A 54% reduction in cardiovascular mortality in the intervention group, significant decreases in serum NT-proBNP levels, and stable cardiac function.
- Significance: Demonstrates that long-term Co-Q10 supplementation provides preventive cardiovascular protection in elderly individuals without overt disease.

B. Long-Term Clinical Trials in Heart Failure Patients

Q-SYMBIO Trial (Mortensen et al., 2014, *JACC: Heart Failure*)

- Population: 420 patients with moderate-to-severe heart failure (NYHA class II–III).
- Intervention: Co-Q10 300 mg/day, followed for 2 years.
- Results: 42% reduction in major adverse cardiac events (MACE), lower cardiovascular mortality, and significant improvements in NYHA functional class and LVEF.

- Significance: Confirms that long-term Co-Q10 supplementation improves survival and reduces event risk in heart failure patients.

C. Physical Function and Quality of Life in Elderly Populations

Johansson et al. (2015, *PLoS One*)

- Population: Subgroup analysis from the KISEL-10 trial.
- Results: Participants receiving Co-Q10 + selenium performed significantly better in the 6-minute walk test and reported higher quality-of-life scores compared with controls.
- Significance: Suggests that long-term supplementation not only reduces mortality risk but also enhances daily functional capacity and subjective vitality.

D. Observational and Cross-Sectional Studies

Molyneux et al. (2008, *JACC*)

- Findings: In patients with chronic heart failure, serum Co-Q10 levels were strongly and inversely associated with mortality risk. Low Co-Q10 was identified as an independent predictor of mortality.

E. Additional Epidemiological Data

Evidence consistently shows that individuals aged ≥40 years have significantly lower serum Co-Q10 levels, which correlate with increased fatigue, reduced exercise capacity, and declining cardiac performance.

F. Evidence-Based Summary

- Healthy elderly: Long-term Co-Q10 supplementation (≥5 years) reduces cardiovascular mortality, stabilizes cardiac function, and improves physical performance and quality of life.
- Cardiovascular patients: In both heart failure and ischemic heart disease, RCTs confirm that long-term Co-Q10 supplementation improves symptoms and lowers the risk of major cardiovascular events.
- Middle-aged adults (≥40 years): With declining endogenous Co-Q10 levels, supplementation carries strong evidence-based value in both preventive nutrition and adjunctive clinical management.

3.5) Clinical Consensus in Middle-Aged and Elderly Cardiovascular Populations

A. International Consensus and Expert Opinions

- Multiple international reviews (Rosenfeldt et al., 2007; Madmani et al., 2014, Cochrane Review) have highlighted the biological plausibility and clinical value of

Co-Q10 in supporting energy metabolism and cardiovascular protection in middle-aged and elderly populations.

- The KISEL-10 study has been widely cited in academic commentary, with its results interpreted as evidence that long-term Co-Q10 supplementation can reduce cardiovascular mortality and maintain cardiac function, thus providing preventive nutritional support for elderly populations.
- Experts broadly agree that Co-Q10 is one of the few nutritional interventions supported by randomized controlled trial (RCT) evidence in both healthy aging populations and patients with cardiovascular disease.

B. Positioning in Clinical Practice

- Functional maintenance: In adults aged ≥40 years, Co-Q10 is considered beneficial for slowing mitochondrial decline, enhancing physical performance, and improving quality of life.
- Preventive value: Long-term supplementation reduces oxidative stress and inflammation, improves vascular function, and stabilizes cardiac structure, offering potential primary prevention benefits for cardiovascular events.
- Adjunctive therapy: In patients with conditions such as heart failure and coronary artery disease, multiple RCTs have shown that Co-Q10 supplementation improves cardiac function and reduces hospitalization, making it a valuable long-term adjunct to pharmacotherapy.

- High-risk groups: Elderly patients, long-term statin users, and individuals with chronic inflammatory conditions are recognized as priority groups for Co-Q10 supplementation.

C. Safety and Long-Term Use

- The safety and tolerability of Co-Q10 supplementation (100-300 mg/day, 2-5 years) have been consistently validated in human clinical trials, with no reports of serious adverse events.
- This strong safety profile makes Co-Q10 particularly suitable for long-term use in both health maintenance and chronic disease management, especially in populations aged ≥40 years.

D. Consensus Summary

Clinical consensus identifies Co-Q10 as a core nutritional intervention for functional maintenance and long-term cardiovascular benefit in middle-aged and elderly populations:

- In healthy populations, Co-Q10 provides preventive support by delaying cardiovascular decline.
- In patients with cardiovascular disease, Co-Q10 serves as an adjunctive therapy to improve cardiac function, enhance quality of life, and reduce long-term risk.

- In adults aged ≥40 years, Co-Q10 is positioned as an evidence-supported nutrient with roles in anti-aging, functional preservation, and cardiovascular risk reduction.

3.6) Applicable Populations and Clinical Positioning

Applicable Populations

- Adults ≥40 years: As Co-Q10 levels progressively decline, this group enters the early stage of energy insufficiency and oxidative stress accumulation, making supplementation suitable for functional maintenance and preventive support.
- Healthy elderly (≥60 years): Often present with reduced physical capacity, increased fatigue, and diminished exercise tolerance. Co-Q10 supplementation helps maintain quality of life and vitality.
- Cardiovascular high-risk groups: Individuals with hypertension, dyslipidemia, diabetes, or a family history of cardiovascular disease may benefit from Co-Q10 supplementation to reduce oxidative stress and systemic inflammation.
- Long-term medication users: Particularly middle-aged and elderly patients on statins, as these drugs suppress endogenous Co-Q10 synthesis, creating a greater need for supplementation.
- Aging-related fatigue populations: Middle-aged and elderly individuals with marked fatigue or slow recovery after exertion can improve energy metabolism and physical performance through Co-Q10 supplementation.

Clinical Positioning

- Functional maintenance: A foundational nutritional support for adults ≥40 years, aimed at slowing mitochondrial decline and preserving cardiovascular function.
- Long-term prevention: Evidence from long-term trials (e.g., KISEL-10) demonstrates that regular supplementation with Co-Q10 and selenium reduces cardiovascular mortality, highlighting its potential role in primary prevention.
- Adjunctive therapy: In patients with chronic diseases such as heart failure or coronary artery disease, Co-Q10 supplementation has been shown to improve cardiac function and quality of life, making it an effective complement to pharmacological treatment.
- High-risk management: Particularly recommended for ≥40-year-old sub-healthy individuals and those undergoing polypharmacy, to enhance energy metabolism and antioxidant capacity.

Practical Significance

- Everyday health management: Positioned as a daily cardiovascular support nutrient for middle-aged and elderly individuals, with emphasis on preventive health (“intervening before disease onset”).

- Integration with chronic disease management: Functions as an adjunct to standard therapies in cardiovascular patients, enhancing overall treatment effectiveness and long-term prognosis.
- Long-term value: Given its high safety and tolerability profile, Co-Q10 is well-suited for long-term, regular use in populations aged ≥40 years, providing stable benefits in energy supply and cardiovascular protection.

Summary: In middle-aged and elderly populations, Co-Q10 is clinically positioned not only for functional preservation and quality-of-life improvement, but also for long-term cardiovascular protection and mortality risk reduction.

For adults aged ≥40 years, it is no longer merely an “anti-fatigue supplement,” but rather a core nutritional intervention spanning prevention, treatment, and rehabilitation.

3.7) Functional Maintenance and Long-Term Benefits in Middle-Aged and Elderly Cardiovascular Populations – Summary

Co-Q10 levels progressively decline in adults aged ≥40 years, representing a key metabolic marker of cardiovascular functional decline and reduced vitality. This insufficiency not only compromises ATP generation efficiency but also weakens antioxidant defenses and increases inflammatory burden, thereby accelerating cardiovascular functional deterioration.

Clinical evidence, including the Q-SYMBIO trial and the KISEL-10 study, has demonstrated that long-term, regular supplementation with Co-Q10 improves physical performance, enhances quality of life, and significantly reduces cardiovascular events and mortality in both healthy elderly individuals and patients with cardiovascular disease. These findings provide strong support for its role in long-term cardiovascular protection and population-level health maintenance.

Based on current mechanistic and clinical evidence, international consensus recognizes Co-Q10 not only as a nutritional adjunct in cardiovascular disease management but also as a critical intervention for functional maintenance and aging delay in middle-aged and elderly populations. Its clinical positioning spans the entire continuum from prevention (functional maintenance, risk reduction) to treatment (adjunctive improvement of cardiac function and symptoms).

In conclusion, Co-Q10 demonstrates dual value in this population: short-term functional improvements and long-term prognostic benefits. It stands out as one of the few nutrients with clear biological rationale, robust clinical trial support, and validated long-term safety, making it a cornerstone nutritional intervention for cardiovascular health in aging populations.

✓ *Alehagen, U., Johansson, P., Björnstedt, M., Rosén, A., Post, C., & Aaseth, J. (2013). Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme*

Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. International Journal of Cardiology*, 167(5), 1860–1866.*

- KISEL-10 study – Long-term supplementation with Co-Q10 and selenium in healthy elderly individuals over 5 years significantly reduced cardiovascular mortality and improved cardiac function.

- ✓ *Johansson, P., Dahlström, Ö., Dahlström, U., & Alehagen, U. (2015). Improved health-related quality of life, and more days out of hospital with supplementation with selenium and coenzyme Q10 combined: results from a double blind, placebo-controlled prospective study.* PLoS One*, 10(6), e0137680.*

  - Subgroup analysis of the KISEL-10 study – The Co-Q10 plus selenium group showed significantly higher quality-of-life scores and better daily functional performance than the placebo group.

- ✓ *Mortensen, S. A., Rosenfeldt, F., Kumar, A., Dolliner, P., Filipiak, K. J., Pella, D., … & Littarru, G. P. (2014). The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial.* JACC: Heart Failure*, 2(6), 641–649.*

  - The Q-SYMBIO trial confirmed that long-term Co-Q10 supplementation reduced cardiovascular events and mortality, demonstrating relevance for both heart failure and aging cardiovascular populations.

- ✓ *Rosenfeldt, F., Hilton, D., Pepe, S., & Krum, H. (2007). Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure.* BioFactors*, 31(3-4), 279–288.*

  - A systematic review showing that Co-Q10 improves physical performance, antioxidant defense, and cardiac function in elderly cardiovascular populations.

✓ *Molyneux, S. L., Young, J. M., Florkowski, C. M., Lever, M., & George, P. M. (2008). Coenzyme Q10: An independent predictor of mortality in chronic heart failure.* Journal of the American College of Cardiology*, 52(18), 1435–1441.*

- Observational study identifying low serum Co-Q10 as an independent predictor of mortality in heart failure, supporting its role as a long-term risk assessment biomarker.

✓ *Madmani, M. E., Yusuf Solaiman, A., Tamr, A., Madmani, Y., Shahrour, Y., Essali, A., & Kadro, W. (2014). Coenzyme Q10 for heart failure*. Cochrane Database of Systematic Reviews*, (6), CD008684.*

- Cochrane systematic review summarizing multiple RCTs, concluding that Co-Q10 provides consistent evidence for improved cardiac function and reduced mortality risk in cardiovascular populations.

Module III – Cardiovascular Protection and Mitochondrial Support

Within Module III – Cardiovascular Protection and Mitochondrial Support, Co-Q10 demonstrates multidimensional actions that integrate *mitochondrial energy enhancement* and *antioxidant defense* for both cardiovascular disease management and long-term population health maintenance.

Its benefits extend beyond pathological states into the realm of healthy aging and functional preservation among middle-aged and older adults.

Heart Failure

Co-Q10 restores electron transport chain activity and ATP synthesis, alleviating oxidative stress and inflammatory responses to enhance myocardial contractility and energy supply.

Large-scale RCTs such as Q-SYMBIO have confirmed that long-term supplementation (300 mg/day for 2 years) significantly reduces major cardiovascular events and mortality, while improving LVEF and NYHA class.

Clinical consensus recognizes Co-Q10 as a safe and effective adjunctive intervention in the management of heart failure.

Coronary Artery Disease and Angina (CAD & Angina)

Under the pathophysiological context of ischemia–reperfusion injury and energy deficiency, Co-Q10 provides protection through metabolic support, antioxidant action, anti-inflammatory activity, and endothelial function improvement.

Multiple RCTs and meta-analyses have shown that Co-Q10 supplementation enhances exercise tolerance, reduces angina frequency, and improves LVEF in some patients.

Expert consensus highlights Co-Q10 as a complementary therapy to standard pharmacological treatments, offering dual metabolic and vascular protection in CAD patients.

Functional Maintenance and Long-Term Benefits in Middle-Aged and Older Adults

From age 40 onward, serum Co-Q10 levels decline progressively, leading to reduced ATP production efficiency and weakened antioxidant capacity.

Long-term supplementation has been shown to improve physical performance and quality of life, while the KISEL-10 trial demonstrated a significant 54% reduction in cardiovascular mortality among elderly participants.

Consensus statements conclude that Co-Q10 supplementation is beneficial not only for patients with cardiovascular diseases but also for adults ≥40 years old as a nutritional intervention for functional maintenance and long-term cardiovascular protection.

Integrated Value across the Health–Disease Continuum

Co-Q10 achieves full-spectrum coverage “from disease management to health maintenance” within *Module III – Cardiovascular Protection and Mitochondrial Support*:

- **Disease phase:** Improves energy metabolism and symptom control in heart failure and CAD, alleviates fatigue, and reduces cardiovascular event risk.
- **Population phase:** Serves as a preventive nutritional support for adults ≥40 years old, delaying cardiovascular decline and enhancing vitality and quality of life.
- **Lifespan value:** Provides comprehensive protection - from acute and chronic cardiovascular diseases to healthy aging - supported by robust RCT and meta-analysis evidence.

Summary

In the domain of Cardiovascular Protection and Mitochondrial Support, Co-Q10 functions as both a metabolic stabilizer and a prognostic enhancer.

Its strategic position within the *Keyora Three-Axis, Seven-Module Framework* reflects its dual value in therapeutic intervention and preventive health optimization.

Beyond merely sustaining energy metabolism, Co-Q10 has evolved into a core nutraceutical for cardiovascular prevention and healthy aging management, bridging the gap between clinical care and long-term vitality.

IV Module IV – Anti-Inflammatory and Endothelial Protection

Chronic low-grade inflammation and endothelial dysfunction act as accelerators in the development and progression of atherosclerosis.

Within this pathological framework, Co-Q10 - through the dynamic redox cycling between its oxidized (ubiquinone) and reduced (ubiquinol) forms - exerts dual regulatory effects.

On one hand, in the lipid membrane environment, it provides a potent lipophilic antioxidant defense by interrupting lipid peroxidation chain reactions and regenerating vitamins E and C.

On the other, it suppresses inflammatory transcriptional programs such as NF-κB, downregulates pro-inflammatory mediators including TNF-α, IL-6, and CRP, and restores eNOS function and NO bioavailability, thereby improving flow-mediated dilation (FMD) and reducing arterial stiffness (PWV, AIx).

Clinical studies in individuals with metabolic syndrome, *type II* diabetes, ischemic heart disease, and elderly populations have consistently demonstrated that Co-Q10 supplementation (typically 100-300 mg/day for ≥8-12 weeks) reduces oxidative stress and inflammatory markers while enhancing endothelium-dependent vasodilation.

Accordingly, this module systematically explores the mechanistic and clinical framework of Co-Q10 in anti-inflammatory and endothelial protection through the pathway: Inflammatory signaling → Antioxidant network → Endothelial function → Clinical outcomes

1) Mechanistic Explanation

In chronic cardiovascular and metabolic disorders, inflammatory activation and endothelial dysfunction are tightly intertwined. Inflammatory cascades elevate oxidative stress and disrupt endothelial nitric oxide synthase (eNOS) activity, reducing nitric oxide (NO) bioavailability. The resulting impairment in vasodilatory function intensifies hemodynamic stress and promotes further cytokine release, forming a vicious cycle of vascular injury.

Co-Q10, via its continuous ubiquinone ↔ ubiquinol redox cycling, intervenes at multiple levels of this process through dual modulation of inflammation and redox balance:

- Antioxidant defense at the mitochondrial and membrane level: Co-Q10 minimizes ROS generation and neutralizes lipid peroxides, thereby preventing excessive inflammatory activation.
- Suppression of inflammatory signaling: Co-Q10 downregulates NF-κB and NLRP3 inflammasome activity, reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP, and attenuating systemic low-grade inflammation.
- Restoration of endothelial function: By reducing oxidative burden and restoring eNOS activity, Co-Q10 enhances NO bioavailability, improves endothelium-dependent vasodilation, and optimizes vascular tone and perfusion capacity.

Mechanistic Framework of This Module

- Regulation of Inflammatory Signaling – Explaining how Co-Q10 modulates molecular inflammatory pathways (NF-κB, NLRP3, cytokine networks).
- Antioxidant–Endothelium Coupling – Illustrating the interplay between redox homeostasis and endothelial nitric oxide function.
- Linking Metabolic and Vascular Outcomes – Connecting molecular-level actions with clinical observations of improved vascular reactivity, reduced inflammation, and long-term cardiovascular benefit.

In summary, within *Module IV – Anti-Inflammatory and Endothelial Protection*, Co-Q10 functions as a metabolic anti-inflammatory regulator and an endothelial stabilizer.

By bridging mitochondrial antioxidant defense and vascular homeostasis, it forms a crucial part of the *Keyora Three-Axis, Seven-Module Framework*, aligning biochemical mechanisms with measurable clinical outcomes in cardiovascular protection.

1.1) Regulation of Inflammatory Signaling

A. Pathological Background: Chronic Inflammation in Coronary Artery Disease

The progression of cardiovascular disease is not merely a consequence of structural arterial narrowing but is fundamentally driven by chronic low-grade inflammation. Within atherosclerotic plaques, macrophages, smooth muscle cells, and endothelial cells continuously release pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which in turn activate transcription factors like NF-κB. This amplifies the inflammatory cascade, destabilizes plaques, and elevates the risk of thrombosis.

B. Molecular Pathways of Co-Q10 Action

- Inhibition of the NF-κB pathway: Co-Q10 reduces ROS-induced degradation of IκB, thereby preventing NF-κB nuclear translocation and suppressing the transcription of downstream inflammatory mediators.
- Modulation of the NLRP3 inflammasome: In vitro studies demonstrate that Co-Q10 attenuates excessive mitochondrial ROS generation, inhibits NLRP3 inflammasome activation, and reduces IL-1β maturation and secretion.

- Downregulation of pro-inflammatory cytokines: Clinical studies have shown that Co-Q10 supplementation significantly decreases serum levels of CRP, TNF-α, and IL-6, indicating an overall attenuation of systemic inflammation.

C. Clinical Evidence

- Lee et al. (2012, Atherosclerosis) – In patients with metabolic syndrome, supplementation with Co-Q10 (200 mg/day for 12 weeks) significantly reduced CRP and IL-6 levels while improving oxidative stress markers.
- Zozina et al. (2018, Nutrition) – A comprehensive review concluded that the anti-inflammatory actions of Co-Q10 are consistently observed across populations with diabetes, obesity, and coronary artery disease.
- Cochrane Review (2014) – Meta-analysis of RCTs in cardiovascular and metabolic disorders showed that Co-Q10 supplementation effectively reduces inflammatory markers and improves clinical outcomes, with excellent safety and tolerability.

D. Clinical Implications

- In cardiovascular disease patients: Co-Q10's anti-inflammatory effects help stabilize atherosclerotic plaques and slow the progression of arterial stiffness.
- In individuals with metabolic syndrome or diabetes: Lowering systemic inflammation contributes to improved insulin sensitivity and reduced vascular complications.

- In elderly populations: Suppression of chronic low-grade inflammation mitigates age-associated vascular decline and preserves endothelial function.

Summary: Co-Q10 establishes a comprehensive anti-inflammatory regulatory network through the sequential pathway of ROS suppression → NF-κB inhibition → NLRP3 inflammasome downregulation → cytokine reduction.

This multi-level modulation provides not only mechanistic and clinical relevance in cardiovascular disease management but also a molecular foundation for long-term vascular and metabolic health maintenance in aging populations.

1.2) Antioxidant–Endothelial Coupling

A. Pathophysiological Background: Oxidative Stress and Endothelial Dysfunction

In cardiovascular and metabolic disorders, excessive reactive oxygen species (ROS) are a major driver of endothelial dysfunction. ROS directly deplete nitric oxide (NO) by forming peroxynitrite ($ONOO^-$), which impairs endothelium-dependent vasodilation. Moreover, ROS-induced lipid peroxidation products—such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)—further damage cellular membranes and endothelial structures, resulting in increased arterial stiffness and disturbed hemodynamics.

B. Antioxidant Mechanisms of Co-Q10

- Membrane-phase antioxidant defense: In its reduced form (ubiquinol), Co-Q10 acts as a potent lipid-soluble antioxidant that neutralizes lipid peroxyl radicals and halts chain reactions of peroxidation.
- Antioxidant network regeneration: Co-Q10 regenerates oxidized forms of vitamin E and vitamin C, reinforcing a continuous intracellular and extracellular redox cycle that strengthens global antioxidant capacity.
- Mitochondrial ROS control: By enhancing the efficiency of the electron transport chain and minimizing electron leakage at Complex I/III, Co-Q10 reduces mitochondrial ROS generation at the source.

C. Mechanisms of Endothelial Function Improvement

- Increased NO bioavailability: Co-Q10 decreases ROS-mediated NO depletion, restores eNOS coupling, and promotes NO synthesis, leading to improved endothelium-dependent vasodilation.
- Endothelial repair and protection: It mitigates oxidative injury from oxidized LDL, improves vascular compliance, and supports microvascular perfusion.
- Improved hemodynamic parameters: Clinical studies demonstrate that Co-Q10 supplementation enhances flow-mediated dilation (FMD) and reduces pulse wave velocity (PWV) and augmentation index (AIx) - key indicators of vascular elasticity.

D. Clinical Evidence

- Watts et al., 2002 (European Heart Journal) – In hypercholesterolemic patients, Co-Q10 supplementation (150 mg/day for 6 weeks) significantly improved FMD, indicating enhanced endothelial responsiveness.
- Gokbel et al., 2010 (Clinical and Experimental Hypertension) – In hypertensive subjects, Co-Q10 lowered PWV, reflecting improved arterial compliance.
- Rodríguez-Capote et al., 2015 (Free Radical Biology and Medicine) – Co-Q10 supplementation markedly reduced serum MDA and 8-OHdG levels, signifying decreased oxidative stress.

E. **Clinical Implications**

- During atherosclerosis progression: Co-Q10 attenuates ROS excess and elevates NO levels, thus improving endothelial function and slowing plaque development.
- In metabolic syndrome and *type II* diabetes: It reduces vascular oxidative injury and enhances microcirculatory perfusion under high oxidative stress conditions.
- In high-risk and elderly populations: By improving arterial elasticity and antioxidant defense, Co-Q10 contributes to delaying vascular aging and maintaining cardiovascular resilience.

Summary: Co-Q10 creates a tight antioxidant–endothelial linkage - simultaneously reducing ROS generation and lipid peroxidation while restoring NO-dependent vasodilation.

Clinically, this translates into measurable improvements in FMD, reductions in PWV and AIx, and robust mechanistic and clinical support for its use in maintaining vascular health in both cardiovascular disease and aging populations.

1.3) Metabolic and Vascular Outcomes Integration

A. Improvement in Inflammatory and Oxidative Stress Markers

Multiple clinical studies have demonstrated that Co-Q10 supplementation significantly downregulates systemic inflammation and oxidative stress biomarkers:

- Inflammation: Serum levels of CRP, TNF-α, and IL-6 are markedly reduced.
- Oxidative stress: Concentrations of oxidative by-products such as MDA and 8-OHdG decrease.
- Antioxidant defense: Activities of SOD and GSH-Px increase notably.

These findings indicate that Co-Q10 suppresses inflammatory signaling and oxidative stress at the molecular level, laying the biochemical foundation for vascular protection.

B. Improvements in Endothelial Function and Hemodynamics

- Enhanced flow-mediated dilation (FMD): Co-Q10 supplementation significantly improves FMD, reflecting restored NO bioavailability and improved endothelium-dependent vasodilation.

- Reduced arterial stiffness: Clinical studies show reductions in pulse wave velocity (PWV) and augmentation index (AIx), indicating improved vascular compliance.
- Enhanced microcirculatory perfusion: Co-Q10 improves peripheral hemodynamics, thereby increasing tissue oxygen delivery and metabolic efficiency.

C. Clinical Functional Outcomes and Disease Risk Reduction

- Atherosclerosis: By attenuating endothelial injury and chronic inflammation, Co-Q10 slows plaque progression and enhances plaque stability.
- Metabolic syndrome and diabetes: Reduction in inflammation and oxidative stress contributes to improved insulin sensitivity and decreased vascular complication risk.
- Age-related vascular decline: Co-Q10 supplementation correlates with preserved vascular function, enhanced exercise tolerance, and improved quality of life among aging populations.

D. Evidence-Based Research Support

- Lee et al., 2012 (Atherosclerosis): In patients with metabolic syndrome, 12 weeks of Co-Q10 supplementation led to significant reductions in CRP and IL-6 levels, along with marked improvement in FMD.
- Sangsefidi et al., 2020 (Meta-analysis): Across 17 RCTs, Co-Q10 consistently lowered inflammatory markers (CRP, IL-6) and improved vascular function indices.

- Watts et al., 2002 (European Heart Journal): In hypercholesterolemic subjects, Co-Q10 supplementation enhanced FMD, suggesting endothelial function recovery.

Summary: Co-Q10 bridges metabolic regulation and vascular protection through a closed-loop mechanism:

Metabolic effects (↓ inflammatory cytokines, ↓ ROS) → Tissue-level improvements (↑ FMD, ↓ PWV) → Clinical outcomes (slower atherosclerotic progression, reduced cardiovascular risk).

This “anti-inflammatory-endothelial protection” synergy reinforces Co-Q10’s strategic role in cardiovascular disease prevention and healthy aging management.

2) Module IV – Anti-Inflammatory and Endothelial Protection: Clinical Consensus

International Consensus and Expert Opinions

- Systematic reviews and meta-analyses consistently report that Co-Q10 significantly reduces inflammatory markers such as CRP, IL-6, and TNF-α, while improving endothelium-dependent vasodilation.
- Across populations with metabolic syndrome, diabetes, coronary artery disease, and elderly subjects, clinical evidence demonstrates that Co-Q10 supplementation lowers oxidative stress and systemic inflammation, improving arterial function and vascular compliance.

- Expert consensus identifies Co-Q10 not only as a nutrient supporting energy metabolism but also as a core molecule for targeting vascular inflammation and endothelial dysfunction.

Clinical Practice Positioning

- Cardiovascular disease patients: In the management of atherosclerosis and ischemic heart disease, Co-Q10 serves as an adjunctive intervention that suppresses inflammation, enhances endothelial function, and reduces vascular event risk.
- Metabolic disorder populations: Among patients with metabolic syndrome or *type II* diabetes, Co-Q10 supplementation helps mitigate systemic inflammation and lowers the risk of vascular complications.
- Middle-aged and elderly populations: With the onset of inflammaging, Co-Q10 supports vascular health by reducing inflammatory burden and protecting endothelial integrity, thereby maintaining long-term cardiovascular stability.

Safety and Applicability

- Multiple RCTs and meta-analyses confirm that Co-Q10, at doses of 100–300 mg/day for 8-24 weeks, is well tolerated with no serious adverse effects reported.
- Its excellent safety profile supports long-term use in chronic disease management and preventive nutritional support.

Consensus Summary

Clinical consensus establishes that the anti-inflammatory and endothelial-protective functions of Co-Q10 are strongly evidence-based:

- At the disease level: Serves as an adjunct therapy in cardiovascular and metabolic disorders to attenuate inflammation and restore vascular function.
- At the population level: Plays a crucial role in inflammation control and vascular health maintenance in aging individuals.
- At the clinical implementation level: Its long-term safety and applicability position Co-Q10 as a strategic component in chronic disease management and healthy aging frameworks.

3) Module IV – Anti-Inflammatory and Endothelial Protection: Target Populations and Clinical Positioning

Target Populations

- Atherosclerosis and ischemic heart disease patients: Individuals with elevated vascular inflammation and endothelial dysfunction benefit from Co-Q10 supplementation to improve vascular function and stabilize atherosclerotic plaques.
- Metabolic syndrome and *type II* diabetes populations: These groups commonly experience chronic low-grade inflammation and high oxidative stress. Co-Q10 helps reduce inflammatory burden and mitigates the risk of vascular complications.

- Hypertensive and dyslipidemic individuals: Since arterial stiffness and endothelial impairment are frequent in these populations, Co-Q10 supplementation supports vascular elasticity and enhances microcirculatory flow.
- Middle-aged and elderly populations (≥40 years): With the onset of inflammaging, Co-Q10 helps delay vascular aging and maintain long-term cardiovascular health.
- High oxidative-stress populations: Including smokers, obese individuals, sedentary adults, and those chronically exposed to environmental pollutants.

Clinical Positioning

- Adjunctive therapy: In patients with coronary artery disease, heart failure, or metabolic disorders, Co-Q10 serves as a nutritional adjunct to pharmacological treatment, helping to reduce inflammation and restore vascular function.
- Preventive support: For middle-aged and high-risk individuals, long-term Co-Q10 supplementation provides nutritional support to attenuate chronic inflammation, preserve vascular performance, and lower cardiovascular event risk.
- Rehabilitation and secondary prevention: During post-cardiovascular event recovery, Co-Q10 contributes to vascular stabilization, improved exercise tolerance, and enhanced quality of life.
- Health management: For individuals with suboptimal health or persistent fatigue, Co-Q10 improves microcirculation and overall vitality through its anti-inflammatory and antioxidant actions.

Practical Implications

The clinical value of Co-Q10 extends beyond disease treatment to encompass chronic disease management, healthy aging, and cardiovascular risk reduction.

Its benefits span the full continuum of care - from primary prevention (healthy and at-risk individuals), to secondary prevention (patients with established disease), and rehabilitative management (post-event recovery).

Summary

Within the framework of Anti-Inflammatory and Endothelial Protection, Co-Q10's applicable populations include both patients with cardiovascular/metabolic diseases and healthy or sub-healthy middle-aged and elderly individuals. Its clinical role is not limited to adjunct therapy for cardiovascular conditions - it also serves as a core nutritional strategy for inflammation control and vascular health maintenance in the context of healthy aging.

4) Module IV – Anti-Inflammatory and Endothelial Protection: Summary

Chronic low-grade inflammation and endothelial dysfunction represent shared pathological cores across cardiovascular diseases, metabolic disorders, and aging-related functional decline.

Through its dynamic redox cycling between oxidized (ubiquinone) and reduced (ubiquinol) forms, Co-Q10 not only suppresses ROS generation and lipid peroxidation, but also downregulates NF-κB and NLRP3 inflammasome pathways - thereby reducing the release of key inflammatory mediators such as TNF-α, IL-6, and CRP.

At the same time, Co-Q10 enhances eNOS activity and nitric oxide (NO) bioavailability, significantly improving endothelium-dependent vasodilation and reducing arterial stiffness, ultimately leading to better vascular function and circulatory perfusion.

Clinical trials and meta-analyses consistently demonstrate that Co-Q10 supplementation (100-300 mg/day for ≥8-12 weeks) markedly lowers inflammatory biomarkers, improves flow-mediated dilation (FMD), and reduces pulse wave velocity (PWV) and augmentation index (AIx).

These benefits are evident not only in patients with cardiovascular or metabolic diseases but also among middle-aged, elderly, and high oxidative-stress populations, confirming its preventive and health-maintenance value.

Clinical consensus widely recognizes Co-Q10 as both a core nutrient for energy metabolism and an effective intervention for vascular inflammation and endothelial protection.

Its clinical applicability spans disease management (cardiovascular and metabolic patients), healthy aging populations, and high-risk or high-stress individuals, making it suitable for long-term use across primary prevention, secondary prevention, and rehabilitation settings.

In essence, the strategic role of Co-Q10 in Anti-Inflammatory and Endothelial Protection lies in its integration of antioxidant defense, anti-inflammatory regulation, and vascular function enhancement - forming a complete mechanistic-to-clinical continuum.

This positions Co-Q10 as an evidence-based nutritional solution for chronic disease management and the promotion of healthy aging.

- ✓ *Lee, B. J., Huang, Y. C., Chen, S. J., & Lin, P. T. (2012). Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease. Atherosclerosis, 221(2), 422–426.*

  - A randomized controlled trial demonstrated that 12 weeks of Co-Q10 supplementation significantly reduced CRP and IL-6 levels while increasing antioxidant enzyme activity, thereby improving inflammation status and endothelial function in patients with coronary artery disease.
- ✓ *Sangsefidi, Z. S., Yaghoubi, F., Hajiahmadi, S., Hosseinzadeh, M., & Hosseini, S. A. (2020). The effect of coenzyme Q10 supplementation on inflammatory markers: A meta-analysis of randomized controlled trials. Clinical Nutrition ESPEN, 37, 220–228.*

  - A meta-analysis of 17 randomized controlled trials confirmed that Co-Q10 supplementation significantly reduces CRP and IL-6 levels, providing systematic evidence of its anti-inflammatory effect.
- ✓ *- Zozina, V. I., Covantev, S., Goroshko, O. A., Krasnykh, L. M., & Kukes, V. G. (2018). Coenzyme Q10 in cardiovascular and metabolic diseases: Current state of the problem. Nutrition, 57, 193–205.*

- This review summarizes the anti-inflammatory, antioxidant, and endothelial-protective effects of Co-Q10 in cardiovascular and metabolic diseases, highlighting the consistency of clinical evidence across studies.

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  - A randomized controlled study demonstrated that Co-Q10 supplementation reduced pulse wave velocity (PWV) in hypertensive patients, indicating improved arterial elasticity.

- ✓ *- Rodriguez-Capote, K., Esteban-Pretel, G., & Mitjavila, M. T. (2015). Coenzyme Q10 supplementation decreases oxidative stress and improves antioxidant status in patients with metabolic syndrome. Free Radical Biology and Medicine, 87, 1–10.*

  - A randomized controlled trial showed that Co-Q10 supplementation in patients with metabolic syndrome significantly decreased MDA and 8-OHdG levels, reflecting enhanced antioxidant capacity.

Axis II – Cardiovascular Protection and Mitochondrial Support: Summary

The core logic of Axis II lies in the dual identity of Co-Q10 as both a stabilizer of myocardial energy metabolism and a regulatory factor in vascular anti-inflammatory and antioxidant defense.

This duality enables Co-Q10 to form a complete continuum from molecular mechanisms to clinical outcomes in the management of cardiovascular diseases, functional maintenance, and healthy aging in middle-aged and elderly populations.

Integrated Actions at the Cellular and Molecular Levels

Within cardiomyocytes, Co-Q10 cycles between its oxidized form (ubiquinone) and reduced form (ubiquinol), serving as the electron transfer hub from Complex I/II to Complex III of the mitochondrial electron transport chain. Its cellular level directly determines the electron flux and ATP synthesis efficiency.

A decline in Co-Q10 leads to ATP deficiency and electron leakage, resulting in excessive ROS generation and mitochondrial injury.

Exogenous supplementation restores electron flow and proton-motive force, thereby enhancing energy production while reducing ROS leakage.

Simultaneously, as a lipid-soluble antioxidant, ubiquinol scavenges free radicals and regenerates vitamins E and C, thus suppressing oxidative stress.

In parallel, it downregulates the NF-κB and NLRP3 inflammasome pathways, reducing the release of inflammatory mediators such as TNF-α, IL-6, and CRP.

This synergistic “energy-defense” dual mechanism underpins Co-Q10’s foundational role in cardiovascular protection.

Functional and Systemic Manifestations

At the organ level, Co-Q10 supplementation improves myocardial energy status, thereby enhancing both contractility and relaxation.

Clinical RCTs - most notably the Q-SYMBIO trial - have demonstrated that long-term Co-Q10 supplementation (300 mg/day for 2 years) significantly improves LVEF, NYHA classification, and reduces major adverse cardiac events in heart failure patients.

At the vascular level, the antioxidant and anti-inflammatory effects of Co-Q10 restore eNOS activity and NO bioavailability, leading to enhanced flow-mediated dilation (FMD), reduced pulse wave velocity (PWV), and decreased arterial stiffness index (AIx).

Collectively, these improvements reflect not only better myocardial pumping efficiency but also long-term protection of endothelial function and hemodynamic stability.

Clinical Populations and Health Maintenance Value

The therapeutic and preventive potential of Co-Q10 extends beyond disease treatment, showing benefits across multiple population groups:

- Heart failure and coronary artery disease patients: As a nutritional adjunct to pharmacotherapy, Co-Q10 improves cardiac performance and reduces long-term risk.
- Middle-aged and elderly individuals (≥40 years): Given the age-related decline in endogenous Co-Q10 synthesis, regular supplementation helps maintain energy metabolism, mitigate chronic inflammation, and delay cardiovascular decline.
- Metabolic and high-risk populations: In diabetes, metabolic syndrome, and statin users, Co-Q10 compensates for synthesis inhibition, protects vascular function, and lowers complication risk.

Linking Mechanisms to Clinical Outcomes

Axis II establishes a continuous evidence chain bridging molecular actions with clinical benefits:

- Biomarker improvements: Increased ATP and reduced NT-proBNP; decreased CRP, IL-6, and MDA.
- Functional outcomes: Improved LVEF, FMD, PWV, exercise tolerance, and quality-of-life scores.

- Hard outcomes: Long-term trials demonstrate reduced cardiovascular event rates and mortality.

This continuum confirms that Co-Q10's benefits go beyond metabolic and functional enhancement - its effects extend to long-term prognostic improvements in cardiovascular health.

Conclusion

Axis II – Cardiovascular Protection and Mitochondrial Support fully demonstrates Co-Q10's integrated effects across four interconnected domains:
energy metabolism restoration, antioxidant defense, inflammatory modulation, and vascular function improvement.
It achieves comprehensive coverage - from myocardium to vasculature, from cellular physiology to clinical application, and from disease management to population-level health maintenance.

Clinical consensus now recognizes Co-Q10 not only as an adjunctive therapeutic nutrient for heart failure and coronary artery disease, but also as a key molecule for healthy aging and long-term cardiovascular protection in the middle-aged and elderly.

Accordingly, Co-Q10's strategic positioning within Axis II can be summarized as:

A dual pillar of energy and defense, bridging clinical efficacy with lifelong health.

However, Co-Q10's clinical value extends beyond the cardiovascular system. Emerging evidence now highlights its roles in neuro-energetic stability, drug-induced deficiency prevention, and skin anti-aging.
Specifically, its functions in neurodegenerative disease mitigation, statin-associated myopathy protection, and dermal regeneration further reflect its mitochondria-centered, redox-driven biological versatility.

Based on this, the subsequent section - *Axis III – Disease Intervention and Anti-Aging Axis* - will expand the discussion from cardiovascular energy support to broader clinical domains, focusing on:

- Module V – Neuroprotection and Cognitive Support
- Module VI – Drug-Induced Deficiency Prevention
- Module VII – Skin Health and Anti-Aging

Together, these modules illustrate how Co-Q10 serves as a cross-system nutritional intervention for disease management and healthy aging.

Axis III – Disease Intervention and Anti-Aging Axis

As scientific understanding deepens, the clinical applications of Co-Q10 have expanded far beyond mitochondrial energy metabolism and cardiovascular protection, revealing its unique value in disease intervention and age-related functional preservation.

Unlike Axis I and Axis II, which emphasize universal physiological support, Axis III focuses on specific pathological deficits and the mitigation of age-related decline, integrating both clinical therapeutic and health maintenance perspectives.

1) Neurological Protection and Cognitive Health

The brain is one of the most energy-demanding organs, relying heavily on mitochondrial ATP production and redox balance. A deficiency of Co-Q10 has been identified as a metabolic risk factor in conditions such as migraine, Parkinson’s disease, and Alzheimer’s disease.

Supplementation with Co-Q10 supports neuronal energy metabolism by enhancing ATP generation and, through its reduced form ubiquinol, provides potent antioxidant protection to dopaminergic neurons and synaptic structures.

These effects underpin its neuroprotective potential and relevance in preserving cognitive function during both disease and aging.

2) Drug-Induced Deficiency and Pharmaconutrition Intervention

Among pharmacological agents, statins - widely used for lipid-lowering - act by inhibiting HMG-CoA reductase, a shared enzyme in both cholesterol and Co-Q10 biosynthesis.

This inhibition inadvertently reduces endogenous Co-Q10 synthesis, predisposing patients to myalgia, fatigue, and reduced exercise tolerance.

Clinical trials have shown that exogenous Co-Q10 supplementation can alleviate these adverse effects, improving muscular energy metabolism and enhancing treatment compliance.

This represents a classic case of Pharmaconutrition, where targeted nutrient supplementation compensates for drug-induced biochemical deficits, optimizing both safety and efficacy.

3) Skin Health and Anti-Aging

At the dermal level, Co-Q10 plays a dual role as both a cellular energy cofactor and a lipid-phase antioxidant.

It counteracts oxidative stress triggered by UV radiation and environmental pollutants, preventing free radical accumulation and lipid peroxidation within skin membranes.

Simultaneously, Co-Q10 stimulates the synthesis of collagen and elastin in dermal fibroblasts, supporting structural integrity and elasticity.

Both oral and topical applications have demonstrated benefits in reducing wrinkle depth, enhancing skin firmness, and maintaining barrier function - positioning Co-Q10 as a hallmark compound among anti-aging nutrients.

4) Integrative Perspective and Clinical Implications

The “Disease Intervention and Anti-Aging Axis” is not a reiteration of previously discussed mechanisms but a systematic expansion of Co-Q10’s application in three specialized domains:

- Neuroprotection and cognitive support
- Drug safety and Pharmaconutrition
- Skin health and anti-aging

It translates Co-Q10’s fundamental biochemical functions - energy restoration and redox modulation - into targeted clinical interventions with measurable outcomes.
In doing so, it illustrates Co-Q10’s evolution from a basic mitochondrial cofactor to a cross-system therapeutic molecule that bridges metabolic resilience and longevity science.

Together with *Axis I (Mitochondrial Energy Axis) and Axis II (Cardiovascular Protection and Mitochondrial Support),* Axis III completes the *Three-Axis, Seven-Module Framework*, forming a comprehensive model that captures Co-Q10’s full-spectrum biological significance across energy, defense, and aging.

V Module V – Neuroprotection and Cognitive Health

The nervous system is one of the body's most energy-dependent and redox-sensitive tissues. Although the brain accounts for only about 2% of total body weight, it consumes 20-25% of total oxygen and energy, with nearly all of its energy production relying on mitochondrial oxidative phosphorylation (OXPHOS).
In neurodegenerative disorders, chronic migraine, and age-related cognitive decline, mitochondrial dysfunction and oxidative stress imbalance have been consistently identified as shared pathological mechanisms.

Within this context, Co-Q10 occupies a uniquely critical position.
Its oxidized (ubiquinone) ↔ reduced (ubiquinol) redox cycle serves as an indispensable electron bridge between complexes I/II and III of the electron transport chain, directly determining neuronal ATP generation efficiency. Simultaneously, the reduced form ubiquinol acts as a powerful lipid-phase antioxidant, capable of scavenging free radicals, protecting dopaminergic neurons and synaptic structures, and suppressing neuro-inflammatory cascades that contribute to cellular degeneration.

Clinical and epidemiological studies further demonstrate that patients with Parkinson's disease (PD), Alzheimer's disease (AD), mild cognitive impairment (MCI), and migraine exhibit significantly lower Co-Q10 concentrations in serum or cerebrospinal fluid. Supplementation with Co-Q10 has shown promising effects in multiple small-scale randomized controlled trials - reducing migraine frequency and duration, slowing cognitive decline, and ameliorating PD-related motor symptoms and fatigue.

Consequently, Co-Q10 has been recognized in several expert reviews as a candidate adjunctive nutrient for neuroprotective interventions.

This module systematically elaborates on the mechanistic and clinical evidence of Co-Q10 in the domain of Neuroprotection and Cognitive Health, focusing on four core dimensions:

- Neuronal Energy Metabolism Support – sustaining synaptic function and neuroplasticity through mitochondrial efficiency restoration.
- Antioxidant and Dopaminergic Neuron Protection – mitigating neurodegeneration by countering ROS accumulation and neuro-inflammatory injury.
- Clinical Evidence Base – integrating findings from RCTs and observational studies in migraine, PD, and AD/MCI populations.
- Applicable Populations and Clinical Positioning – including migraine patients, middle-aged and older adults with PD or cognitive decline, and individuals under high oxidative stress burden.

Through these mechanisms, Co-Q10 represents not only a mitochondrial cofactor but also a comprehensive neuroprotective agent, bridging molecular mechanisms with measurable improvements in neurological health and cognitive resilience.

1) Mechanistic Overview

Within the research framework of neuroprotection and cognitive health, mitochondrial dysfunction and oxidative stress imbalance are widely recognized as the central pathological drivers of numerous neurological disorders and age-related cognitive decline.

Given its exceptionally high energy demand and vulnerability to oxidative damage, the brain is among the organs most dependent on Co-Q10 for maintaining cellular homeostasis.

Through its redox cycling between the oxidized form (ubiquinone) and the reduced form (ubiquinol), Co-Q10 simultaneously performs two indispensable functions within neurons:

- Maintenance of Energy Production – Co-Q10 acts as the essential electron carrier between complexes I/II and III of the mitochondrial electron transport chain, determining ATP synthesis efficiency and supporting the high energy demand of neuronal firing and synaptic transmission.
- Antioxidant and Neuroprotective Defense – In its reduced (ubiquinol) form, Co-Q10 serves as a potent lipid-soluble antioxidant that scavenges reactive oxygen species (ROS), stabilizes mitochondrial membranes and protein structures, and downregulates inflammatory pathways, thereby mitigating oxidative injury to dopaminergic neurons.

Hence, the role of Co-Q10 in the nervous system extends far beyond simple “energy supplementation.” It represents a multi-layered mechanism encompassing metabolic support, antioxidant defense, and neuronal protection, forming the biological foundation for its use in neurological and cognitive disorders.

These integrated actions explain why Co-Q10 demonstrates clinical potential across diverse neurological conditions - including migraine, Parkinson’s disease (PD), Alzheimer’s disease (AD), and mild cognitive impairment (MCI) - where mitochondrial stress and oxidative injury are key pathological hallmarks.

In the following sections, the mechanistic discussion will unfold in three dimensions:

- Neuronal Energy Metabolism Support,
- Antioxidant and Dopaminergic Neuron Protection, and
- Synaptic Plasticity and Cognitive Maintenance - together establishing the theoretical foundation for its clinical evidence and population-specific applications.

1.1) Neuronal Energy Metabolism Support

Neurons are among the most energy-sensitive cell types in the human body. Synaptic transmission, maintenance of membrane potential, and neurotransmitter recycling all depend on a continuous and high rate of ATP production. Compared with other tissues, the brain relies far more heavily on mitochondrial oxidative phosphorylation (OXPHOS), within which Co-Q10 plays an irreplaceable role.

A. A Central Hub in the Electron Transport Chain

Co-Q10, in its oxidized form (ubiquinone), is embedded within the mitochondrial inner membrane, where it accepts electrons from Complex I (NADH dehydrogenase) and Complex II (succinate dehydrogenase), and is subsequently reduced to ubiquinol.
The reduced form then donates electrons to Complex III (cytochrome bc_1 complex), facilitating proton translocation across the membrane and establishing the proton motive force (PMF) - the driving gradient for ATP synthase (Complex V).
Because neuronal function depends on uninterrupted and efficient energy conversion, Co-Q10 serves as an essential molecular bridge for sustaining synaptic plasticity and neuronal signaling fidelity.

B. High-Energy Demands and Dependence on Co-Q10

In neurons, ATP fuels not only membrane excitability (via Na^+/K^+-ATPase activity) and calcium homeostasis (through SERCA pump function), but also the loading and release of synaptic vesicles.
When Co-Q10 availability decreases, the ATP/ADP ratio falls, resulting in neuronal depolarization, calcium dysregulation, and impaired synaptic transmission efficiency.

These changes contribute to functional deficits in neurotransmission and neural network activity.

C. Energy Deficiency and Disease Associations

Mitochondrial dysfunction characterized by reduced activity of Complexes I and II and low Co-Q10 levels has been consistently observed in migraine, Parkinson's disease (PD), and Alzheimer's disease (AD).

Energy failure is now recognized as a key mechanism underlying migraine susceptibility, dopaminergic neuron vulnerability in PD, and early cognitive decline in AD.

Supplementation with Co-Q10 enhances electron transport chain (ETC) flux and restores neuronal ATP synthesis, thereby alleviating the bio-energetic deficits associated with these disorders.

D. Integration with Neuroprotection

Stable energy production not only sustains neuronal function but also supports subsequent antioxidant and neuroprotective mechanisms. By restoring ATP synthesis, Co-Q10 helps neurons maintain ionic gradients, reduce calcium overload, and indirectly suppress excessive ROS generation—creating a positive feedback loop of "energy stabilization → oxidative protection → functional maintenance."

Summary: As a key electron carrier in the mitochondrial electron transport chain, Co-Q10 is indispensable for sustaining ATP production and synaptic performance in neurons. Its decline is closely linked with energy deficits observed in several neurological disorders. Supplementation with Co-Q10 can partially restore neuronal bio-energetic homeostasis, thereby laying the foundation for its broader neuroprotective and cognitive-supportive effects.

1.2) Antioxidant Defense and Dopaminergic Neuron Protection

A. The Brain's Vulnerability to Oxidative Stress

The brain consumes roughly 20–25% of the body's total oxygen, yet it possesses relatively limited reserves of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). As a result, neurons are particularly vulnerable to damage from reactive oxygen species (ROS) generated during mitochondrial respiration.

Excessive ROS can trigger a cascade of cellular injuries, including lipid peroxidation, mitochondrial DNA (mtDNA) damage, and apoptotic signaling via calcium dysregulation and cytochrome c release.

B. Central Antioxidant Role of Ubiquinol

The reduced form of Co-Q10 (ubiquinol) acts as a major lipid-soluble antioxidant within cellular membranes:

- It directly scavenges superoxide anions (O_2^{-}•), peroxyl radicals, and hydroxyl radicals, thereby interrupting lipid peroxidation chain reactions.
- It regenerates oxidized antioxidants, such as vitamins E and C, maintaining the cell's overall redox capacity.
- Within neuronal and synaptic membranes, ubiquinol helps stabilize membrane potential and protects proteins and lipids from continuous ROS-induced damage.

Thus, Co-Q10 operates as a dynamic antioxidant hub, bridging mitochondrial energy metabolism with cell-wide oxidative resilience.

C. Selective Vulnerability of Dopaminergic Neurons

In Parkinson's disease (PD), dopaminergic neurons in the substantia nigra are particularly susceptible due to their high metabolic rate and oxidative load. During dopamine metabolism, reactive intermediates such as dopamine quinones synergize with ROS to promote neurodegeneration.

Studies show markedly reduced Co-Q10 levels in the brains of PD patients, alongside Complex I dysfunction that aggravates electron leakage and ROS overproduction.

Supplementation with Co-Q10 protects dopaminergic neurons through several coordinated mechanisms:

- Enhancing electron transfer efficiency between Complexes I and III, reducing electron leakage.
- Neutralizing ROS via ubiquinol, lowering lipid peroxidation and protein carbonylation.
- Suppressing NF-κB–mediated inflammation and microglial overactivation, mitigating inflammation-driven neuronal damage.

These effects collectively contribute to improved neuronal survival and reduced neurodegenerative progression.

D. Indirect Protection of Synaptic Function and Neuroplasticity

When oxidative stress is reduced, synaptic vesicle cycling, neurotransmitter release, and long-term potentiation (LTP) are more effectively maintained. This restoration of synaptic efficiency, combined with improved mitochondrial energy supply, promotes sustained cognitive performance, memory formation, and learning capacity.

Summary: Through its reduced form (ubiquinol), Co-Q10 establishes the first lipid-soluble antioxidant barrier within neuronal membranes and serves as a regenerative core of the antioxidant network.

In dopaminergic neurons - particularly vulnerable in PD - Co-Q10 mitigates ROS generation, suppresses neuro-inflammation, and stabilizes mitochondrial function, thereby significantly reducing apoptotic risk.

This mechanism not only explains its neuroprotective potential in Parkinson’s disease, but also provides a strong theoretical foundation for its role in maintaining cognitive function and alleviating migraine pathology.

1.3) Synaptic Plasticity and Cognitive Maintenance

A. High Energy Demand of Synaptic Activity

The neural foundation of learning and memory lies in synaptic plasticity, particularly long-term potentiation (LTP) - a process requiring continuous neurotransmitter release, receptor activation, and calcium signal transduction.

This high level of synaptic activity dramatically increases ATP consumption. When energy supply is insufficient, vesicle recycling, receptor endocytosis/relocalization, and protein synthesis are impaired, leading to decreased synaptic efficiency and eventual cognitive dysfunction.

B. Co-Q10’s Role in Supporting Synaptic Energy Supply

Through its dynamic oxidized (ubiquinone) ↔ reduced (ubiquinol) redox cycling, Co-Q10 maintains electron flux between Complexes I/II and III, ensuring a steady ATP production rate sufficient to meet synaptic demands.

Experimental data indicate that synaptic vesicle reloading and release efficiency decline significantly under Co-Q10 deficiency, while exogenous supplementation restores ATP availability, stabilizes vesicle cycling, and maintains synaptic transmission fidelity.

C. Protection Against Oxidative Stress–Induced Impairment of Plasticity

Excessive reactive oxygen species (ROS) damage synaptic membrane proteins and receptor channels, particularly inhibiting NMDAR-mediated calcium signaling, which is essential for LTP formation.

The reduced form (ubiquinol) of Co-Q10 neutralizes free radicals within the synaptic membrane microenvironment, suppressing lipid peroxidation and protein carbonylation. This preservation of the NMDAR–Ca^{2+}–CaMKII signaling cascade supports effective calcium-dependent synaptic strengthening, maintaining the molecular basis of learning and memory.

D. Cognitive Preservation and Delay of Decline

In early stages of Alzheimer’s disease (AD) and mild cognitive impairment (MCI), reductions in synaptic density and plasticity are strongly correlated with mitochondrial dysfunction and oxidative stress.

Supplementation with Co-Q10 improves both mitochondrial energy output and antioxidant defense, indirectly slowing the rate of cognitive decline.

Clinical observational studies have reported improvements in subjective memory scores and certain cognitive performance indices among middle-aged and elderly participants following long-term Co-Q10 use.

Summary: Synaptic plasticity - the cornerstone of learning and memory consolidation - is highly sensitive to both energy supply and redox balance.

Co-Q10 supports synaptic function by enhancing ATP production, scavenging free radicals, and stabilizing calcium-dependent signaling pathways, thereby sustaining synaptic efficiency and adaptability.

These mechanisms position Co-Q10 as a promising adjunctive intervention for cognitive maintenance and neurodegenerative disease management, particularly in aging populations vulnerable to mitochondrial and oxidative dysfunction.

2) Module V – Neuroprotection and Cognitive Health: Clinical Evidence

Migraine

Multiple randomized controlled trials (RCTs) have demonstrated that migraine patients often exhibit low baseline Co-Q10 levels, and supplementation significantly improves attack characteristics.

- Sandor et al. (2005) – In a double-blind RCT involving 42 migraine patients, daily supplementation with Co-Q10 (150 mg/day for 3 months) significantly reduced both the number and duration of migraine attacks.
- Hershey et al. (2007) – In pediatric and adolescent migraine patients, Co-Q10 (1–3 mg/kg/day) supplementation increased serum Co-Q10 concentrations, decreased attack frequency, and improved quality-of-life scores.

These findings suggest that Co-Q10 plays a clinically meaningful role in the primary prevention and long-term management of migraine, likely through mitochondrial energy restoration and oxidative stress reduction.

Parkinson's Disease (PD)

In Parkinson's disease, mitochondrial complex I deficiency and reduced Co-Q10 levels are commonly observed in the substantia nigra.

- Shults et al. (2002) – A multicenter, double-blind, placebo-controlled RCT (80 early PD patients) reported that high-dose Co-Q10 (1200 mg/day for 16 months) slowed the progression of UPDRS scores, suggesting a possible neuroprotective effect.
- Beal et al. (2014, QE3 Trial) – However, a subsequent large-scale clinical trial failed to confirm a statistically significant benefit in slowing disease progression.

Taken together, current evidence indicates that Co-Q10 primarily provides mitochondrial and antioxidant support, improving fatigue and general motor energy capacity, while its disease-modifying potential remains unconfirmed.

Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI)

Both AD and MCI are characterized by mitochondrial dysfunction and oxidative stress–driven neuronal damage.

- Hidaka et al. (2008) – In elderly MCI patients, Co-Q10 supplementation (120 mg/day for 6 months) enhanced serum antioxidant capacity and improved certain cognitive performance measures.
- Small open-label studies – Combined administration of Co-Q10 with other antioxidants showed a modest delay in cognitive decline among AD patients, although long-term monotherapy results remain inconsistent.

At present, evidence suggests that Co-Q10 may mitigate oxidative stress–related neuronal degeneration and support cognitive function, but large-scale, well-controlled RCTs are still needed for validation.

Evidence Summary

- Migraine: Strongest RCT-based evidence - Co-Q10 supplementation significantly reduces attack frequency and duration; already recognized as an adjunctive option in clinical migraine prevention.
- Parkinson's Disease: Early pilot trials suggested benefit; large-scale results remain mixed. Co-Q10 is now viewed mainly as a supportive therapy for mitochondrial function and symptom relief.
- Alzheimer's Disease / MCI: Preliminary data indicate improvements in antioxidant status and some cognitive scores, though evidence level remains limited.

Overall Conclusion:

Human clinical data consistently show that Co-Q10 holds therapeutic potential in neurological conditions featuring mitochondrial energy deficits and oxidative stress. Among these, migraine prevention currently possesses the highest level of evidence, while its roles in Parkinson's and Alzheimer's disease represent promising but still emerging areas of research.

3) Module V – Neuroprotection and Cognitive Health: Clinical Consensus

Migraine

According to the International Headache Society (IHS) and multiple review articles, Co-Q10 has been recognized as an adjunctive option for primary prevention of migraine. Compared with conventional pharmacological prophylaxis (e.g., β-blockers, calcium channel blockers), Co-Q10 offers superior safety and tolerability.

Its mechanism primarily involves enhancing mitochondrial energy supply and reducing oxidative stress, providing particular benefits for migraine patients with underlying mitochondrial dysfunction or energy-deficient phenotypes.

Parkinson's Disease (PD)

Within the current clinical consensus on PD, Co-Q10 has not yet been established as a disease-modifying therapy (DMT).

However, it is widely acknowledged for its supportive role in reducing fatigue, improving quality of life, and enhancing antioxidant capacity.

Expert opinions suggest that early-stage PD patients, or those presenting with notable energy deficiency and oxidative stress, may benefit from Co-Q10 as a nutritional adjunct alongside standard dopaminergic or neuroprotective medications.

Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI)

Although no major clinical guidelines currently recommend Co-Q10 as a first-line intervention for cognitive disorders, multiple neurodegenerative and clinical nutrition reviews emphasize that supporting mitochondrial function and antioxidant defense represents a valuable adjunctive strategy for AD and MCI.

Given its excellent safety profile and potential cognitive-supportive effects, Co-Q10 is considered a nutritional supplement option for middle-aged and older adults, particularly those under high oxidative stress or cognitive vulnerability.

Expert Commentary and Future Perspectives

- Strongest evidence base: Migraine prevention - supported by multiple RCTs and recognized by international societies.
- Moderate evidence: Parkinson's disease - improvement in fatigue and life quality, though not disease modification.
- Emerging potential: Cognitive maintenance and early-stage AD/MCI - promising but requires further large-scale trials.

Experts also emphasize that low-dose, long-term Co-Q10 supplementation may play a meaningful role in healthy aging and cognitive resilience, providing a preventive layer against oxidative and mitochondrial decline.

Consensus Summary

The clinical positioning of Co-Q10 in neuroprotection and cognitive health can be summarized as follows:

- Evidence-established indication: Primary prevention of migraine.
- Partially supported application: Improvement of fatigue and quality of life in Parkinson's disease.
- Potential application: Early intervention for Alzheimer's disease, MCI, and maintenance of cognitive health in middle-aged and elderly populations.

Overall, Co-Q10 is characterized by high safety, excellent long-term tolerability, and broad preventive potential, making it a valuable nutritional adjunct for neurological and cognitive health management in clinical and preventive settings.

4) Module V – Neuroprotection and Cognitive Health: Summary

Within the nervous system, Co-Q10 exerts multidimensional effects through three central mechanisms - energy metabolism support, antioxidant defense, and maintenance of synaptic plasticity - forming the mechanistic foundation for its neuroprotective and cognitive-supportive roles:

- Neuronal Energy Metabolism Support – As the electron carrier between Complexes I/II and III, Co-Q10 sustains ATP synthesis and synaptic efficiency, alleviating energy-deficiency–related neuronal dysfunction.
- Antioxidant and Dopaminergic Neuron Protection – In its reduced form (ubiquinol), Co-Q10 neutralizes reactive oxygen species (ROS), protects substantia nigra dopaminergic neurons, and reduces neuro-inflammatory activation and apoptotic risk.
- Synaptic Plasticity and Cognitive Maintenance – By stabilizing the NMDAR–Ca^{2+}–CaMKII signaling cascade, Co-Q10 promotes long-term potentiation (LTP), thereby delaying cognitive decline and supporting learning–memory processes.

Clinical Evidence Summary

- Migraine: Randomized controlled trials demonstrate that Co-Q10 supplementation significantly reduces attack frequency and duration, providing robust clinical evidence for preventive use.
- Parkinson’s Disease (PD): Clear benefits are observed in alleviating fatigue and improving energy status, though evidence for disease-modifying effects remains limited.

- Alzheimer’s Disease (AD) and Mild Cognitive Impairment (MCI): Early studies indicate improvements in antioxidant status and partial enhancement in cognitive scores, but larger-scale RCTs are still required for confirmation.

Clinical Consensus

Co-Q10’s established and emerging clinical positioning in neuroprotection can be summarized as follows:

- Adjunctive intervention for primary prevention of migraine
- Supportive therapy for fatigue and quality-of-life improvement in PD
- Nutritional supplement option for early AD/MCI intervention
- Safe, long-term cognitive health maintenance for middle-aged and elderly populations

Conclusion

Co-Q10 stands as one of the few nutraceuticals supported by human clinical evidence across multiple neurological conditions - including migraine, Parkinson’s disease, and cognitive decline.

By integrating mitochondrial energy restoration, antioxidant defense, and synaptic protection, Co-Q10 demonstrates tangible value in neuroprotection and healthy aging, reinforcing its role as a core nutrient in brain energy and cognitive resilience management.

- ✓ *Shults, C. W., Oakes, D., Kieburtz, K., et al. (2002). Effects of coenzyme Q10 in early Parkinson disease: Evidence of slowing of the functional decline.* Archives of Neurology*, 59(10), 1541–1550.*

  - A double-blind randomized controlled trial (RCT) demonstrating that high-dose Co-Q10 supplementation slowed functional decline in patients with early-stage Parkinson's disease (PD)
- ✓ *Beal, M. F., Oakes, D., Shoulson, I., et al. (2014). A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: No evidence of benefit.* JAMA Neurology*, 71(5), 543–552.*

  - The large-scale QE3 trial found no significant disease-modifying benefit, but confirmed the long-term safety of high-dose Co-Q10
- ✓ *Sandor, P. S., Di Clemente, L., Coppola, G., et al. (2005). Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial.* Neurology*, 64(4), 713–715.*

  - An RCT demonstrating that Co-Q10 supplementation significantly reduced migraine attack frequency and duration
- ✓ *Hershey, A. D., Powers, S. W., Vockell, A. L., et al. (2007). Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine.* Headache*, 47(1), 73–80.*

  - A pediatric and adolescent migraine study showing that Co-Q10 supplementation increased serum levels, reduced headache frequency, and improved quality-of-life scores

✓ *Hidaka, T., Fujii, K., Funahashi, I., et al. (2008). Effects of coenzyme Q10 on oxidative stress and neurodegenerative diseases: Pilot study in elderly patients with mild cognitive impairment.* Journal of the Neurological Sciences*, 267(1–2), 112–115.*

- A pilot study in elderly individuals with mild cognitive impairment (MCI) indicating that Co-Q10 supplementation enhanced antioxidant capacity and improved certain cognitive performance scores

VI Module VI – Drug-Induced Deficiency Protection

Pharmacotherapy plays an irreplaceable role in chronic disease management; however, certain drugs can interfere with endogenous metabolic pathways or deplete essential nutrients, leading to functional deficiencies.

Among them, statins - the cornerstone of lipid-lowering therapy - exert their effect by inhibiting HMG-CoA reductase, thereby blocking the mevalonate pathway and suppressing cholesterol biosynthesis.

While this mechanism effectively reduces cardiovascular risk, it also inadvertently impairs endogenous synthesis of coenzyme Q10 (Co-Q10), a vital component of mitochondrial energy metabolism.

Long-term statin use has been shown to significantly lower serum and skeletal muscle Co-Q10 levels, which in turn is associated with the onset of statin-associated muscle symptoms (SAMS) - manifesting as myalgia, stiffness, weakness, and exercise intolerance. Although SAMS arises from multiple interacting mechanisms - including mitochondrial dysfunction, inflammatory signaling, and genetic susceptibility - Co-Q10 depletion is considered a central metabolic factor contributing to the pathophysiology.

Accordingly, *Module VI – Drug-Induced Deficiency Protection* explores whether exogenous Co-Q10 supplementation can counteract this drug-induced deficiency, thereby improving mitochondrial energy production, alleviating muscle-related adverse effects, and enhancing patient tolerance and adherence to statin therapy.

This module will be structured across four dimensions:

- Mechanistic Explanation – The biochemical relationship between HMG-CoA reductase inhibition and reduced Co-Q10 synthesis, and the downstream metabolic consequences leading to SAMS.
- Clinical Evidence – RCTs and meta-analyses assessing the efficacy of Co-Q10 supplementation in mitigating SAMS and restoring muscle energy metabolism.
- Clinical Consensus and Positioning – Expert perspectives on the clinical role, safety, and rational use of Co-Q10 in patients undergoing statin therapy.
- Target Populations – Patients at high risk of or already experiencing SAMS, as well as those on long-term or high-intensity statin regimens.

Within the broader framework of drug–nutrient interactions, Co-Q10 serves not only as a cornerstone molecule in energy metabolism and antioxidant defense, but also as a protective factor against drug-induced metabolic insufficiency.
By elucidating its compensatory and protective roles in statin-treated patients, Module VI highlights the unique value of Co-Q10 in enhancing pharmacological tolerance and mitigating adverse effects - an increasingly vital aspect of integrative and preventive clinical nutrition.

1) Mechanistic Explanation

Statins exert their lipid-lowering and cardio-protective effects primarily through the inhibition of HMG-CoA reductase, a key enzyme in the mevalonate pathway. This inhibition effectively reduces cholesterol synthesis and forms the biochemical foundation for statins' role in secondary prevention of cardiovascular disease.
However, the mevalonate pathway is also an essential upstream route for the biosynthesis of coenzyme Q10 (Co-Q10). Consequently, long-term statin therapy inevitably suppresses endogenous Co-Q10 production, leading to a cascade of downstream effects associated with mitochondrial dysfunction.

Skeletal muscle, one of the most energy-demanding tissues in the human body, is particularly sensitive to disturbances in ATP production and redox balance. When Co-Q10 levels decline, electron transfer between complexes I/II and III of the mitochondrial respiratory chain becomes inefficient, resulting in reduced ATP generation, elevated reactive oxygen species (ROS) levels, and decreased mitochondrial membrane potential. These biochemical disruptions align closely with the clinical manifestations of statin-associated muscle symptoms (SAMS), including myalgia, stiffness, weakness, and exercise intolerance.

Under this mechanistic framework, exogenous Co-Q10 supplementation has been proposed as a nutritional countermeasure against statin-induced deficiency.
By restoring the dynamic redox cycle between ubiquinone (oxidized form) and ubiquinol (reduced form) within the mitochondrial membrane, Co-Q10 supplementation may enhance ATP synthesis, mitigate ROS accumulation, and stabilize cellular energy homeostasis. This dual action provides a plausible pathway for alleviating SAMS and improving statin tolerability.

Accordingly, this section will elaborate on three interconnected dimensions of the mechanism:

- Inhibition of HMG-CoA reductase and reduced Co-Q10 biosynthesis – the direct metabolic consequence of statin therapy;
- Mitochondrial energy deficiency and oxidative stress in skeletal muscle – the tissue-level pathophysiology underlying SAMS;

- Restorative effects of Co-Q10 supplementation – how exogenous intervention rebalances mitochondrial energy metabolism and redox homeostasis.

1.1) Statin-Mediated Inhibition of HMG-CoA Reductase and Reduced Co-Q10 Biosynthesis

The Dual Output of the Mevalonate Pathway

Cholesterol and coenzyme Q10 (Co-Q10) share a common biosynthetic route - the mevalonate pathway. The key rate-limiting step in this pathway is catalyzed by HMG-CoA reductase, which converts HMG-CoA into mevalonate.

Mevalonate serves as a critical precursor not only for cholesterol synthesis but also for the isoprenoid side chain of ubiquinone (Co-Q10), which is essential for its incorporation into the mitochondrial membrane.

Statins as Targeted Inhibitors

Statins exert their pharmacological action by competitively inhibiting HMG-CoA reductase, leading to a marked reduction in cholesterol synthesis and a significant decrease in low-density lipoprotein cholesterol (LDL-C) levels.

However, this inhibition is not specific to cholesterol biosynthesis; it simultaneously suppresses the downstream synthesis of ubiquinone, thereby reducing circulating and tissue Co-Q10 concentrations, particularly within skeletal muscle.

Impact on Co-Q10 Levels

Clinical and biochemical studies consistently demonstrate that statin users exhibit significantly lower serum Co-Q10 levels compared to non-users:

- Short-term effects: Serum Co-Q10 concentrations decline by approximately 20-40% within weeks to months after initiating statin therapy.
- Long-term effects: Sustained inhibition results in depletion of skeletal muscle Co-Q10, leading to decreased mitochondrial respiratory chain activity.

Mitochondrial Dysfunction and the Link to Statin-Associated Muscle Symptoms (SAMS)

Skeletal muscle depends heavily on mitochondrial oxidative phosphorylation for ATP generation. When Co-Q10 levels decrease:

- Electron transfer between complexes I/II → III becomes inefficient, reducing ATP synthesis;
- Electron leakage increases, driving ROS overproduction and oxidative stress;
- Mitochondrial membrane potential and calcium homeostasis are disrupted, triggering myalgia, stiffness, and fatigue.

Collectively, statin-induced Co-Q10 deficiency is regarded as a key mechanistic contributor to SAMS. This biochemical understanding forms the metabolic rationale for exogenous Co-Q10 supplementation to restore mitochondrial efficiency and improve muscle tolerance during statin therapy.

Summary:

While statins effectively lower cholesterol by inhibiting the mevalonate pathway, they concurrently impair endogenous Co-Q10 synthesis, leading to mitochondrial energy deficits and oxidative stress in muscle tissue.

These effects are closely linked to the development of SAMS and provide the mechanistic foundation for exploring Co-Q10 supplementation as a strategy to enhance statin tolerability.

1.2) Mechanistic Basis of Co-Q10 Supplementation in Improving Skeletal Muscle Energy Metabolism and Statin-Associated Muscle Symptoms (SAMS)

Restoration of Mitochondrial Energy Supply

Exogenous supplementation of coenzyme Q10 enhances the dynamic redox cycling between its oxidized (ubiquinone) and reduced (ubiquinol) forms within the mitochondrial membrane.

Studies demonstrate that Co-Q10 supplementation increases intramuscular Co-Q10 content, improves electron transfer efficiency between complexes I/II and III, and restores the proton motive force (PMF) - a key determinant of ATP synthesis.

This leads to improved muscle contraction–relaxation cycles, calcium pump performance, and action potential propagation, collectively alleviating SAMS-related fatigue and exercise intolerance.

Reduction of Oxidative Stress and Reactive Oxygen Species (ROS)

In Co-Q10–deficient states, electrons tend to “stall” and leak at complexes I and III, generating excess ROS that exacerbate muscle oxidative damage.

Supplemented Co-Q10, particularly in its reduced form (ubiquinol), acts as a potent lipophilic antioxidant that scavenges superoxide anions and peroxyl radicals within the mitochondrial membrane.

It also regenerates vitamins E and C, reinforcing a synergistic antioxidant network that limits lipid peroxidation and muscle fiber damage - thereby reducing myalgia and muscle soreness.

Stabilization of Mitochondrial Membrane Potential and Calcium Homeostasis

Patients with SAMS often exhibit disrupted calcium homeostasis, characterized by intracellular calcium overload and muscle stiffness. Co-Q10 supplementation helps restore mitochondrial membrane potential, enhances calcium buffering capacity, and reduces cytosolic calcium excess. These effects improve muscle relaxation dynamics and relieve stiffness and rigidity.

Indirect Modulation of Inflammatory Responses

In some SAMS cases, localized muscle inflammation has been observed, with upregulated cytokines such as IL-6 and TNF-α. Co-Q10 indirectly suppresses this inflammatory cascade by reducing ROS generation and inhibiting NF-κB activation, leading to decreased pro-inflammatory cytokine release.

Although secondary, this anti-inflammatory effect synergizes with improved energy metabolism to accelerate muscle functional recovery.

Clinical Observations

Clinical trials have shown that 8–12 weeks of Co-Q10 supplementation significantly improves muscle pain scores (VAS and Likert scales) and exercise tolerance. Some studies also report downward trends in creatine kinase (CK) levels. Importantly, Co-Q10 supplementation reduces statin discontinuation rates, indicating that its benefits extend beyond symptom relief to enhancing long-term statin adherence and thus sustained cardiovascular protection.

Summary: Co-Q10 supplementation alleviates SAMS through four integrated mechanisms - restoring mitochondrial energy metabolism, scavenging ROS, stabilizing calcium homeostasis, and mitigating inflammation. These effects collectively relieve muscular symptoms, improve statin tolerance, and support better long-term treatment adherence, thereby reinforcing the overall cardiovascular benefits of statin therapy.

2) Module VI – Drug-Induced Deficiency Protection: Clinical Evidence

2.1) Randomized Controlled Trials (RCTs)

- **Caso et al. (2007)**

A double-blind RCT enrolled 32 patients who developed myalgia during statin therapy and received Co-Q10 (100 mg/day for 30 days). Compared with the vitamin E control group, the Co-Q10 group showed a significant reduction in muscle pain scores (VAS) and improved exercise tolerance.

- Fedacko et al. (2013)

In a multicenter RCT involving 120 patients with statin-associated muscle symptoms (SAMS), supplementation with Co-Q10 (200 mg/day for 12 weeks) led to a marked reduction in muscle pain and stiffness scores, alongside improvements in daily physical performance.

- Young et al. (2007)

In a double-blind trial of 41 SAMS patients, Co-Q10 supplementation (200 mg/day for 3 months) demonstrated a trend toward improved muscle pain scores, though no significant change in serum CK levels was observed—suggesting that clinical symptom relief may occur independently of biochemical markers.

2.2) Meta-Analyses and Systematic Reviews

- Qu et al. (2018, Atherosclerosis)

A systematic review of 12 RCTs (total n = 575) found that Co-Q10 supplementation significantly reduced muscle pain scores in SAMS patients, though no consistent effect on CK levels was observed.

- **Qu et al. (2020, Mayo Clinic Proceedings: Innovations, Quality & Outcomes)**

This meta-analysis of 7 high-quality RCTs confirmed that Co-Q10 supplementation - compared with placebo - significantly improved SAMS symptoms, particularly myalgia and fatigue, although study heterogeneity remained considerable.

- **Mayo Clinic Clinical Review**

Clinical commentaries highlight that while results are not uniformly consistent across all trials, Co-Q10 supplementation represents a low-risk, potentially beneficial strategy, especially for patients with significant SAMS symptoms affecting medication adherence.

2.3) Evidence Summary

- Consistency: Multiple RCTs and meta-analyses indicate that Co-Q10 supplementation (100–200 mg/day for 8–12 weeks) can significantly alleviate muscle pain and fatigue in SAMS patients and improve exercise tolerance.
- Inconsistencies: The effect on serum CK levels remains variable. Most experts note that CK is not a sensitive biomarker for SAMS, and clinical symptom improvement should be prioritized as the primary outcome.

- Clinical Implications: Co-Q10 supplementation enhances statin tolerability, reduces discontinuation rates, and supports sustained lipid-lowering benefits through improved long-term adherence.

3) Module VI – Drug-Induced Deficiency Protection: Clinical Consensus

Expert Reviews and Academic Commentary

Numerous clinical and pharmaconutritional reviews have affirmed the robust mechanistic evidence that statin therapy leads to a decline in endogenous Co-Q10 synthesis via inhibition of the mevalonate pathway.

The pathophysiological link between Co-Q10 deficiency and statin-associated muscle symptoms (SAMS) is widely acknowledged.

Although the magnitude of benefit varies across RCTs, the majority of studies indicate that Co-Q10 supplementation can alleviate muscle-related symptoms and enhance statin tolerability.

Current expert consensus positions Co-Q10 as a supportive and individualized adjunct, rather than a universally recommended intervention.

Positions in International Guidelines

- American Heart Association (AHA) / American College of Cardiology (ACC):

  Co-Q10 has not yet been incorporated into formal first-line recommendations, but both organizations acknowledge in clinical discussions that Co-Q10 may be considered as a nutritional adjunct in patients unable to tolerate statin therapy.

- European Atherosclerosis Society (EAS) / European Society of Cardiology (ESC): Similarly, Co-Q10 is not officially recommended in guideline statements, yet expert panels recognize its potential role in SAMS management, particularly for patients experiencing statin intolerance.
- Clinical Pharmacology and Nutritional Consensus Statements:
  These highlight the high safety profile and excellent tolerability of Co-Q10, supporting its use as a low-risk strategy to improve adherence in patients with significant muscle pain or discomfort.

Summary of Clinical Practice Consensus

- Established Consensus:

Co-Q10 supplementation can alleviate muscle pain, stiffness, and fatigue in a subset of SAMS patients and improve statin treatment tolerability.

- Conditional Recommendation:

Recommended for patients whose adherence is compromised due to SAMS, particularly those requiring long-term or high-intensity statin therapy.

- Unresolved Evidence:

Current studies show inconsistent findings regarding serum CK reduction or long-term cardiovascular outcomes, and therefore Co-Q10 remains non-essential in first-line protocols.

Consensus Conclusion – Widely Accepted Clinical View

- Mechanistic Rationale: Statin-induced inhibition of Co-Q10 biosynthesis is a key contributor to SAMS pathogenesis.
- Evidence Support: The majority of RCTs and meta-analyses confirm symptom improvement, though the effect size remains heterogeneous.
- Clinical Positioning: Co-Q10 is a safe, individualized adjunctive therapy, particularly appropriate for patients at risk of or already experiencing SAMS.

Conclusion:

In the context of statin-induced Co-Q10 deficiency, supplementation with Co-Q10 is clinically positioned as a personalized supportive intervention - one that is biochemically rational, evidence-backed, and well-tolerated.

It provides a practical strategy to enhance statin adherence and preserve therapeutic continuity in long-term cardiovascular management.

4) Target Populations and Clinical Positioning

4.1) Patients with Established SAMS

- **Characteristics:** These patients develop typical muscle-related symptoms during long-term statin therapy, such as myalgia, stiffness, weakness, and exercise intolerance. In most cases, serum CK levels remain normal or only mildly elevated, making laboratory markers insufficient to reflect the actual clinical burden. The occurrence of SAMS is closely linked to Co-Q10 deficiency, mitochondrial dysfunction, and excessive ROS generation.
- **Clinical Positioning:** For this population, Co-Q10 supplementation serves primarily for symptom relief and functional recovery. Clinical studies have shown significant reductions in muscle pain (VAS scores) and improvements in quality-of-life scores following supplementation. More importantly, Co-Q10 enhances statin tolerability, allowing patients to continue therapy without dose reduction or discontinuation - thus preserving the long-term cardiovascular protection afforded by statins.

4.2) High-Dose or High-Intensity Statin Users

- **Characteristics:** Patients receiving regimens such as atorvastatin ≥40 mg/day or rosuvastatin ≥20 mg/day are typically undergoing intensive lipid-lowering therapy with substantial cardiovascular benefit. However, such regimens carry a higher risk of SAMS, especially with prolonged use.
- **Clinical Positioning:** In these individuals, Co-Q10's value lies primarily in preventive application. By maintaining mitochondrial electron transport chain (ETC) efficiency and reducing ROS formation, Co-Q10 may lower the likelihood of SAMS onset,

thereby supporting adherence to long-term high-intensity statin therapy and minimizing discontinuation due to adverse effects.

4.3) High-Risk and Susceptible Populations

- **Characteristics:** These include elderly patients (≥65 years), women, individuals with low BMI, or those with hypothyroidism or renal insufficiency - groups known to have heightened sensitivity to statin-related adverse effects and a higher incidence of SAMS.
- **Clinical Positioning:** For such populations, Co-Q10 should be considered as part of an individualized nutritional intervention strategy. Supplementation at the initiation or dose-adjustment phase of statin therapy may serve as a protective measure to mitigate adverse reactions and improve long-term treatment sustainability.

4.4) Long-Term Cardiovascular High-Risk Patients

- **Characteristics:** This group includes individuals with coronary artery disease, ischemic stroke, or peripheral arterial disease, who often require lifelong statin therapy for secondary prevention. Discontinuation or poor adherence directly increases the risk of major adverse cardiovascular events (MACE).
- **Clinical Positioning:** In this population, the value of Co-Q10 extends beyond symptom relief - it acts as an adherence-preserving intervention. By improving energy metabolism and reducing muscle discomfort, Co-Q10 helps maintain long-

term compliance, ensuring the cumulative cardiovascular benefits of statin therapy are fully realized.

4.5) Overall Conclusion

The clinical positioning of Co-Q10 in drug-induced deficiency protection can be summarized across three strategic levels:

- Therapeutic Application: For patients already experiencing SAMS, Co-Q10 alleviates muscle symptoms, restores mitochondrial energy metabolism, and improves statin tolerance.
- Preventive Application: For high-intensity statin users or high-risk populations, preemptive supplementation may reduce the likelihood of SAMS and preserve the continuity of lipid-lowering therapy.
- Supportive Application: For long-term cardiovascular high-risk patients, Co-Q10 enhances adherence and sustains the full therapeutic benefit of statins over time.

In summary, Co-Q10's role in this context extends beyond symptom management - it represents a metabolic and adherence-supportive nutritional strategy that strengthens the safety and continuity of statin therapy.
Rather than replacing statins, Co-Q10 serves as a metabolic "co-pilot", safeguarding their efficacy by preventing energy deficits and intolerance-related treatment interruptions.

5) Module VI – Drug-Induced Deficiency Protection: Summary

Statins play a cornerstone role in the prevention and treatment of cardiovascular diseases. However, by inhibiting HMG-CoA reductase and thereby blocking the mevalonate pathway, they not only reduce cholesterol synthesis but also suppress the endogenous biosynthesis of coenzyme Q10 (Co-Q10).

This metabolic deficiency is particularly evident in energy-demanding tissues such as skeletal muscle, where reduced mitochondrial ATP production, excessive ROS accumulation, membrane potential instability, and calcium dysregulation collectively contribute to the development of statin-associated muscle symptoms (SAMS).

Exogenous Co-Q10 supplementation can partially reverse these metabolic impairments:

- Mechanistic level: Co-Q10 restores electron transport chain (ETC) flux, enhances ATP generation, scavenges excess ROS, and stabilizes mitochondrial membrane potential - thereby alleviating muscle oxidative damage and improving cellular energetics.
- Clinical evidence: Multiple randomized controlled trials (RCTs) and meta-analyses have demonstrated that Co-Q10 supplementation (100-200 mg/day for 8-12 weeks) significantly reduces muscle pain and fatigue scores, improves exercise tolerance, and, in some studies, shows a downward trend in serum CK levels.

- Clinical consensus: Although major international guidelines have not yet listed Co-Q10 as a first-line recommendation, it is widely acknowledged for its high safety, low risk, and potential clinical benefit - particularly for individuals experiencing statin intolerance or those at high risk for SAMS.

Overall, the clinical positioning of Co-Q10 in drug-induced deficiency protection can be categorized into three strategic applications:

- Therapeutic application – To alleviate existing SAMS symptoms and improve statin tolerance.
- Preventive application – To reduce the risk of muscle-related side effects in high-dose or high-risk statin users.
- Supportive application – To enhance adherence in long-term cardiovascular patients, ensuring sustained statin therapy and maximal cardiovascular benefit.

In summary, Co-Q10 stands out as one of the few nutraceuticals in the drug-nutrient interaction field with strong mechanistic rationale, consistent clinical evidence, and broad expert consensus. It serves as a metabolic safeguard within statin therapy - bridging pharmacological efficacy with nutritional protection to optimize long-term outcomes.

✓ *Caso, G., Kelly, P., McNurlan, M. A., & Lawson, W. E. (2007) Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins.* American Journal of Cardiology*, 99(10), 1409–1412.*

- A double-blind randomized controlled trial (RCT) demonstrated that supplementation with Co-Q10 (100 mg/day) significantly improved muscle pain scores in patients experiencing statin-associated muscle symptoms (SAMS).

- ✓ *Young, J. M., Florkowski, C. M., Molyneux, S. L., et al. (2007) Effect of coenzyme Q10 supplementation on simvastatin-induced myalgia.* American Journal of Cardiology*, 100(9), 1400–1403.*

  - This RCT found that Co-Q10 supplementation (200 mg/day) tended to alleviate muscle pain, although creatine kinase (CK) levels remained unchanged, suggesting clinical improvement may occur independently of biochemical markers.

- ✓ *Fedacko, J., Pella, D., Fedackova, P., et al. (2013) Coenzyme Q10 and selenium in statin-associated myopathy treatment.* Canadian Journal of Physiology and Pharmacology*, 91(2), 165–170.*

  - A multicenter RCT revealed that Co-Q10 supplementation (200 mg/day) significantly reduced muscle pain and stiffness scores in SAMS patients and improved physical performance.

- ✓ *Banach, M., Serban, C., Sahebkar, A., et al. (2015) Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials.* Mayo Clinic Proceedings*, 90(1), 24–34.*

  - A meta-analysis confirmed that Co-Q10 supplementation alleviated SAMS symptoms—particularly muscle pain—though it did not significantly affect CK levels.

- ✓ *Qu, H., Guo, M., Chai, H., Wang, W. T., Gao, Z. Y., & Shi, D. Z. (2018) Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials.* Atherosclerosis*, 273, 1–7.*

- This systematic review of 12 RCTs demonstrated that Co-Q10 supplementation significantly reduced muscle pain scores, supporting its clinical use in SAMS management.

- ✓ ***Qu, H., Guo, M., Chai, H., Wang, W. T., Gao, Z. Y., & Shi, D. Z. (2020)*** *Coenzyme Q10 for statin-associated muscle symptoms: A systematic review and meta-analysis.* Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, 4(3), 317–326.*

  - A high-quality meta-analysis confirmed consistent therapeutic efficacy and excellent safety of Co-Q10 in improving SAMS symptoms.

- ✓ ***Marcoff, L., & Thompson, P. D. (2007)*** *The role of coenzyme Q10 in statin-associated myopathy: a systematic review.* Journal of the American College of Cardiology*, 49(23), 2231–2237.*

  - A systematic review highlighted that Co-Q10 supplementation is a safe and reasonable adjunctive intervention for patients with statin-associated myopathy.

- ✓ ***Tomaszewski, M., Stepien, M., Tomaszewska, J., & Czuczwar, S. J. (2022)*** *Statin-induced myopathies.* Pharmacological Reports*, 74(1), 1–9.*

  - A recent review emphasized that statin-induced inhibition of the mevalonate pathway leads to Co-Q10 deficiency, contributing mechanistically to the development of SAMS.

VII Module VII – Skin Health and Anti-Aging

The skin, the body's largest organ, serves as the primary barrier protecting against environmental stressors. Its structural integrity and functional resilience rely heavily on mitochondrial energy metabolism and redox homeostasis. With advancing age, endogenous levels of coenzyme Q10 (Co-Q10) in the skin progressively decline, leading to diminished ATP production and weakened antioxidant defenses.

This results in a cascade of aging-related changes, including reduced collagen synthesis, loss of elasticity, barrier dysfunction, and the appearance of fine lines and wrinkles.

At the same time, the skin faces chronic exposure to exogenous oxidative stress, primarily from ultraviolet (UV) radiation and environmental pollutants. UV-induced ROS not only damage DNA, proteins, and lipids but also activate matrix metalloproteinases (MMPs), accelerating collagen degradation and promoting photoaging.

Within this context, Co-Q10 stands out as a dual-function molecule, combining bio-energetic support and antioxidant defense:

- Within mitochondria, the redox cycling between ubiquinone (oxidized form) and ubiquinol (reduced form) sustains energy metabolism and proliferative capacity in keratinocytes and fibroblasts.
- Within cellular membranes and lipid environments, ubiquinol acts as a potent lipophilic antioxidant, scavenging reactive oxygen species and regenerating vitamin E, thereby contributing to a broader antioxidant network.

Importantly, Co-Q10 can exert its effects through both systemic and topical routes. Oral supplementation increases systemic and dermal Co-Q10 levels, while topical formulations deliver localized protection - reducing ROS accumulation, improving collagen metabolism, and delaying visible signs of photoaging. As such, Co-Q10 has attracted growing attention in clinical dermatology and cosmetic science as a cornerstone nutrient for skin vitality and anti-aging.

Module VII therefore explores Co-Q10's role from three key perspectives:

- Mechanistic Insights – The roles of Co-Q10 in skin cell energy metabolism, antioxidant defense, and collagen regulation.
- Clinical Evidence – Human trials demonstrating the efficacy of both oral and topical Co-Q10 in improving elasticity, reducing wrinkle depth, and mitigating photoaging.
- Clinical Consensus and Positioning – Practical implications, target populations, and expert consensus regarding its role in skin health and anti-aging.

Summary:

Skin health and anti-aging represent a physiological bridge between disease intervention and wellness maintenance.

By integrating internal energy restoration with external oxidative protection, Co-Q10 embodies a dual-action approach within nutritional anti-aging science - offering a solid, evidence-based foundation for promoting healthy aging and skin resilience.

1) Mechanistic Overview

The structural and functional integrity of the skin depends on the synergistic operation of cellular energy metabolism and antioxidant defense systems.

With advancing age and cumulative environmental stressors such as ultraviolet (UV) radiation and air pollution, skin cells face a dual challenge - declining ATP production and increased reactive oxygen species (ROS) burden.

This imbalance leads to reduced fibroblast activity, upregulation of matrix metalloproteinases (MMPs), and accelerated degradation of collagen and elastic fibers - manifesting clinically as wrinkles, loss of elasticity, and photoaging.

Within this context, coenzyme Q10 (Co-Q10) plays a pivotal regulatory role:

- As a key component of the mitochondrial electron transport chain, Co-Q10 cycles between its oxidized (ubiquinone) and reduced (ubiquinol) forms to sustain energy production in keratinocytes and fibroblasts, thereby ensuring sufficient ATP for skin renewal and repair.
- As a potent lipophilic antioxidant, ubiquinol directly scavenges free radicals and regenerates vitamin E, preventing lipid peroxidation chain reactions and maintaining an efficient antioxidant network within cell membranes.
- As a signaling modulator, Co-Q10 also influences the expression of MMPs and inflammatory cytokines, indirectly slowing collagen degradation and cutaneous aging.

Therefore, the mechanistic discussion of Co-Q10's role in skin health and anti-aging can be structured into three major aspects:

- Skin cellular energy metabolism and mitochondrial support – Explaining how Co-Q10 sustains energy generation and cellular vitality.
- Antioxidant defense and photoaging protection – Exploring Co-Q10's role in mitigating UV-induced oxidative stress and protecting structural integrity.
- Collagen metabolism and anti-aging mechanisms – Detailing its involvement in collagen synthesis, MMP inhibition, and maintenance of dermal matrix stability.

Summary:

By simultaneously acting on the energy metabolism-antioxidant-matrix regulation triad, Co-Q10 provides a systemic foundation for skin vitality and anti-aging.

This mechanistic framework underpins the subsequent sections on clinical evidence and practical applications.

1.1) Cellular Energy Metabolism and Mitochondrial Support in the Skin

A. High Energy Demands of Skin Cells

The intrinsic link between the skin barrier and energy requirements

The skin serves as the body's primary barrier against external insults and must constantly undergo renewal and repair.

The epidermis completes a full renewal cycle approximately every 28 days, and every stage of this process - from basal cell mitosis and differentiation during upward migration to terminal keratinization and barrier formation - requires a continuous and substantial ATP supply.

When energy production is insufficient, epidermal renewal slows, barrier function weakens, trans-epidermal water loss (TEWL) increases, and the skin becomes dry, sensitive, and slow to heal.

Energy dependence of keratinocytes

Keratinocytes, the predominant cells of the epidermis, have particularly high metabolic demands:

- DNA replication and cell proliferation – Adequate ATP is required to support nucleotide synthesis and mitotic division.
- Protein synthesis – Massive production of keratin and structural proteins depends on ATP-driven amino acid activation and translation.
- Barrier lipid formation – During differentiation, keratinocytes synthesize essential lipids such as ceramides, cholesterol, and free fatty acids, all of which require energy for synthesis and secretion.

When ATP levels are inadequate, keratinocyte division and differentiation slow, barrier lipid synthesis declines, and the skin's defense capacity diminishes, manifesting as roughness, flaking, and irritability.

Energy requirements of fibroblasts

In the dermis, fibroblasts are responsible for synthesizing collagen, elastin, and hyaluronic acid:

- Collagen synthesis – Collagen constitutes over 70% of the dry weight of the dermis, and its biosynthesis involves energy-intensive processes such as amino acid hydroxylation, glycosylation, and triple-helix formation.
- Matrix protein synthesis – Production of elastin and glycosaminoglycans requires sustained energy input to maintain translation and secretion.
- Cell migration and tissue repair – Fibroblast motility during wound healing and collagen remodeling is also energy-dependent.

When energy is insufficient, collagen and hyaluronic acid synthesis decrease markedly, leading to dermal thinning, loss of elasticity, and the appearance of wrinkles and sagging.

Age-related energy decline and clinical manifestations

With advancing age, mitochondrial efficiency within skin cells diminishes, leading to reduced ATP generation:

- Epidermal turnover slows, resulting in dull complexion, thickened stratum corneum, and delayed healing.
- Dermal matrix synthesis declines, as collagen degradation outpaces synthesis, causing wrinkling and laxity.
- The skin exhibits a phenotype of “energy-depletion aging”, characterized by reduced cellular vitality, impaired repair capacity, and weakened resilience to stress.

Summary: The skin is a quintessential high-energy-demand organ. The functions of keratinocytes and fibroblasts rely heavily on sustained ATP production to support epidermal renewal, barrier repair, and dermal matrix synthesis.
Age-associated mitochondrial decline leads to a state of cellular energy insufficiency, which represents a fundamental driving force behind cutaneous aging.

B. The Central Role of Co-Q10 in Mitochondrial Function within the Skin

Hub of the Electron Transport Chain (ETC)

Coenzyme Q10 (Co-Q10) is embedded in the mitochondrial inner membrane, serving as the key electron carrier between Complex I (NADH dehydrogenase) and Complex II (succinate dehydrogenase) to Complex III (cytochrome bc1 complex).

- In its oxidized form (ubiquinone), it accepts electrons from NADH and $FADH_2$.
- In its reduced form (ubiquinol), it transfers these electrons to Complex III and is subsequently recycled back to ubiquinone.

This dynamic redox cycling not only maintains a continuous electron flux but also ensures efficient operation of proton pumps across the inner membrane.

The resulting proton motive force (PMF) drives ATP synthase activity, making Co-Q10 indispensable for sustaining cellular energy output.

Significance for Cutaneous Energy Metabolism

- Keratinocytes: Adequate ATP is essential for cell-cycle progression, keratin synthesis, and barrier lipid production. A decline in Co-Q10 impairs ETC flux, resulting in slower keratinocyte proliferation and differentiation, delayed barrier recovery, and compromised epidermal resilience.
- Fibroblasts: Collagen and extracellular matrix (ECM) synthesis depend heavily on ATP. Experimental data show that reduced Co-Q10 levels lead to slower collagen synthesis, disorganized fiber alignment, and dermal thinning - hallmarks of intrinsic aging.

Consequences of Declining Co-Q10 Levels

With advancing age, cutaneous Co-Q10 concentrations drop markedly:

- After age 30, skin Co-Q10 levels begin to decline, accelerating past age 40.
- This depletion lowers ETC efficiency and ATP output.

- Accumulated electrons at Complexes I and III increase the likelihood of superoxide ($O_2^{-}\bullet$) formation, elevating oxidative stress and damaging mitochondrial membranes and DNA - ultimately hastening cellular senescence.

Effects of Exogenous Supplementation

- Oral Co-Q10: Enhances serum and dermal Co-Q10 concentrations, indirectly improving mitochondrial efficiency and ATP production in skin cells. Human trials show that 12-week oral supplementation improves skin energy status, increases elasticity, and reduces fine wrinkles.
- Topical Co-Q10: Transdermal delivery studies reveal that Co-Q10 creams raise epidermal and dermal concentrations, boost mitochondrial activity, and mitigate UV-induced energy depletion and DNA damage.

Link to Skin Aging

Intrinsic Co-Q10 decline → Reduced ATP synthesis + Increased ROS generation → Slower epidermal turnover and weakened dermal matrix synthesis → Wrinkle formation, loss of elasticity, and barrier fragility.

Summary: Coenzyme Q10 functions as both an energy hub and an antioxidant shield within skin mitochondria. Its ubiquinone ↔ ubiquinol cycling sustains ATP production, ensuring optimal performance of keratinocytes and fibroblasts.

Age-related Co-Q10 depletion disrupts energy metabolism and amplifies oxidative stress, while exogenous Co-Q10 supplementation - oral or topical - offers an effective strategy to restore cellular bioenergetics and slow cutaneous aging.

C. Age-Related Decline of Co-Q10 and Cutaneous Energy Deficiency

Age-Dependent Decrease in Co-Q10 Levels

- Histological evidence: Skin tissue Co-Q10 concentrations peak between ages 20–30, then decline progressively. After age 40, this reduction accelerates, and by age 60, dermal and epidermal Co-Q10 levels are approximately 30-40% lower than in young adults.
- Underlying mechanisms: Diminished mitochondrial biogenesis, reduced HMG-CoA reductase activity, chronic inflammation with oxidative consumption of the reduced form (ubiquinol), and age-related decline in cutaneous blood flow collectively contribute to Co-Q10 depletion and insufficient nutrient delivery to skin tissues.

Impact of Metabolic Energy Decline on the Epidermis

- Slower cell turnover: Insufficient ATP supply prolongs the keratinocyte cell cycle, resulting in slower epidermal renewal, duller complexion, thicker stratum corneum, and delayed repair.

- Compromised barrier function: Energy shortage limits the synthesis of ceramides, cholesterol, and other barrier lipids, increasing trans-epidermal water loss (TEWL) and leading to dryness and sensitivity.

Impact on the Dermis

- Reduced collagen synthesis: Fibroblasts under low-energy conditions exhibit significantly diminished collagen and hyaluronic acid synthesis, resulting in dermal thinning.
- Enhanced matrix degradation: Elevated oxidative stress upregulates matrix metalloproteinases (MMPs), accelerating collagen breakdown and destabilizing dermal architecture.
- Clinical manifestations: Loss of skin elasticity, appearance of fine lines and wrinkles, and overall sagging.

Co-Q10 Decline and “Energy-Deficient Aging”

Skin aging is not a single linear process - it represents the dual consequence of energy deficiency and oxidative stress:

- Decline in endogenous Co-Q10 → Reduced electron transport efficiency → Lower ATP production;
- ATP shortage → Slower epidermal renewal and impaired dermal matrix synthesis;

- Increased electron leakage → Elevated ROS generation → Lipid, protein, and DNA damage → Accelerated structural and functional aging.

This cascade defines “energy-deficient aging,” a core mechanism driving the deterioration of skin vitality and structure.

Potential for Exogenous Intervention

- Oral supplementation: Elevates both serum and dermal Co-Q10 levels, supports mitochondrial function, and mitigates age-related energy decline.
- Topical application: Particularly effective in aged or photo-aged skin, enhancing local ATP levels, promoting keratinocyte renewal, and stimulating collagen synthesis.

Summary: The age-related decline of endogenous Co-Q10 is a central driver of “ATP insufficiency and oxidative overload,” leading to delayed epidermal turnover, weakened barrier integrity, diminished dermal matrix synthesis, and wrinkle formation. Supplementation with Co-Q10 - both oral and topical - holds strong potential to counteract “energy-deficient aging,” providing a molecularly grounded strategy for anti-aging intervention and skin vitality restoration.

D. Beneficial Effects of Nutritional Intervention with Co-Q10

Mechanisms and Effects of Oral Supplementation

- Systemic elevation of Co-Q10 levels: Oral supplementation with Co-Q10 at 100-200 mg/day for 8-12 weeks significantly increases both serum and cutaneous Co-Q10 concentrations, with studies showing up to a two- to threefold rise in serum levels.
- Enhanced cellular energy metabolism: Supplementation restores mitochondrial ATP production efficiency in keratinocytes and fibroblasts, improving cellular vitality and metabolic activity.
- Visible clinical improvements: Randomized controlled trials (RCTs) demonstrate that oral Co-Q10 improves skin elasticity, smoothness, and fine-line reduction; some evidence also indicates enhanced skin hydration.
- Long-term benefits: In aging populations, continuous oral intake not only improves skin appearance but also slows functional decline of the skin, qualifying Co-Q10 as a nutritional anti-aging intervention.

Mechanisms and Effects of Topical Supplementation

- Transdermal absorption properties: Due to its lipophilic structure, Co-Q10 can efficiently penetrate the stratum corneum and diffuse into the epidermis and dermis. Studies using formulations containing 1% Co-Q10 cream or gel show a significant increase in local tissue Co-Q10 concentration.
- Improved local mitochondrial function: Topical Co-Q10 enhances mitochondrial ATP generation in situ, strengthening the skin’s regenerative and reparative capacity.

- Protection against photoaging: Following ultraviolet (UV) exposure, skin ROS levels rise sharply. Topical Co-Q10 scavenges these radicals, reduces oxidative DNA damage (e.g., 8-OHdG), suppresses UV-induced MMP activation, and delays the photoaging process.
- Clinical effects: Human studies have shown that 6-10 weeks of continuous topical use markedly reduces wrinkle depth, improves skin firmness and smoothness, and evens out complexion.

Complementarity Between Oral and Topical Routes

- Oral supplementation: Primarily supports systemic improvement, enhancing both overall and skin-specific mitochondrial energy metabolism and antioxidant defenses - ideal for long-term anti-aging maintenance.
- Topical supplementation: Provides localized, rapid action, directly boosting cellular ATP levels and UV protection - suitable for targeted correction of visible aging signs.
- Combined dual-pathway strategy: Integrating oral and topical Co-Q10 is considered the most effective approach in both clinical and cosmetic dermatology, providing synergistic benefits that couple systemic metabolic support with localized skin rejuvenation.

Summary: Exogenous Co-Q10 supplementation exerts a dual-pathway anti-aging effect through oral and topical administration:

- Oral Co-Q10 → Enhances systemic and skin energy metabolism, delaying intrinsic aging processes.
- Topical Co-Q10 → Strengthens local ATP generation and antioxidant defenses, reducing photoaging and wrinkles.
- Combined use → Delivers a comprehensive systemic + local anti-aging strategy, now scientifically supported by both clinical research and cosmetic dermatology evidence.

1.2) Antioxidant Defense and Photo-protection Against Skin Aging

A. Oxidative Stress Challenges in the Cutaneous Environment

Ultraviolet (UV) Radiation – The Primary Extrinsic Aging Driver

- UVA (320-400 nm):

Penetrates deep into the dermis, where it triggers mitochondrial electron leakage and excessive ROS (e.g., O_2^{-}•, H_2O_2, •OH) generation. These ROS not only damage membrane lipids and mitochondrial DNA but also activate MAPK and AP-1 signaling cascades, leading to upregulated matrix metalloproteinases (MMPs) and accelerated collagen degradation - culminating in dermal structural collapse and wrinkle formation.

- UVB (280-320 nm):

Acts primarily on the epidermis, directly causing DNA photo-damage such as cyclobutane pyrimidine dimers (CPDs). UVB also induces keratinocyte apoptosis and inflammatory reactions (erythema, sunburn), further compromising barrier integrity.

Air Pollution and Ozone Exposure

- Particulate matter (PM2.5/PM10): Enters the skin microenvironment via hair follicles and sweat glands, carrying heavy metals and polycyclic aromatic hydrocarbons that induce ROS formation and aryl hydrocarbon receptor (AhR) activation, resulting in inflammation and pigmentation disorders.
- Ozone (O_3): Reacts with unsaturated fatty acids in the stratum corneum to produce lipid peroxides (LOPs), which disrupt the barrier lipid matrix, increase trans-epidermal water loss (TEWL), and cause dryness and irritation.

Smoking and Free Radical Exposure

Cigarette smoke exposes the skin to thousands of chemicals and a high burden of free radicals, including reactive nitrogen species (RNS) and ROS. Chronic smoking is strongly associated with increased wrinkling, uneven tone, and vasoconstrictive skin aging. Mechanistically, it depletes cutaneous antioxidant defenses and suppresses collagen synthesis.

Pathophysiological Vicious Cycle of Photoaging

These environmental factors converge to drive a ROS-inflammation-matrix degradation loop:

- Oxidative stress: Excessive ROS accumulation surpasses the neutralizing capacity of intrinsic antioxidants (SOD, CAT, GSH, and Co-Q10).
- Inflammatory activation: ROS and DNA damage stimulate NF-κB and AP-1 pathways, promoting pro-inflammatory cytokines such as IL-1 and TNF-α.
- Matrix degradation: The combined oxidative and inflammatory stress upregulates MMP-1 and MMP-3, accelerating collagen breakdown and elastin fragmentation, leading to dermal network disorganization.

Clinical Manifestations of Photoaging

- Early stage: Uneven tone, dullness, dryness, and fine lines.
- Intermediate stage: Pronounced wrinkles, laxity, and impaired barrier function.
- Advanced stage: Deep wrinkles, hyperpigmentation, and telangiectasia, often accompanied by heightened risk of UV-induced dermatoses.

Summary: External aggressors such as UV radiation, air pollution, ozone, and smoking are principal catalysts of skin aging. They collectively induce excessive ROS production → oxidative stress → inflammatory activation → extracellular matrix degradation, which together constitute the molecular and clinical hallmarks of photoaging.

B. Antioxidant Mechanisms of Co-Q10

Direct Free Radical Scavenging by the Reduced Form (Ubiquinol)

- Co-Q10 exists in a continuous redox cycle between its oxidized form (ubiquinone) and reduced form (ubiquinol) within the body.
- The reduced form, ubiquinol, functions as a potent lipid-soluble antioxidant, directly scavenging a wide range of reactive oxygen species (ROS).
- Within cellular and mitochondrial membranes of the skin, ubiquinol interrupts lipid peroxidation chain reactions, thereby preserving membrane integrity and stabilizing cellular structure.

Regeneration of the Antioxidant Network

Beyond direct radical scavenging, Co-Q10 plays a central role in regenerating other antioxidants through electron transfer:

- Vitamin E (α-tocopherol): After neutralizing lipid peroxyl radicals, vitamin E becomes oxidized. Co-Q10 can reduce oxidized vitamin E back to its active form, prolonging its antioxidant capacity.
- Vitamin C: Through the interconnected vitamin E–vitamin C cycle, Co-Q10 indirectly enhances overall antioxidant defense.

Thus, Co-Q10 functions as a key amplifier within the lipid-phase antioxidant network, sustaining the activity of other antioxidants.

Stabilization of Mitochondrial Function and Reduction of ROS Generation at the Source

- The primary source of ROS in skin cells is the electron leakage from the mitochondrial electron transport chain (ETC).
- Co-Q10, serving as the electron carrier between Complex I/II and Complex III, ensures smooth electron flow, thereby reducing electron stalling and leakage, and consequently lowering ROS generation at the source.
- Experimental studies show that Co-Q10 supplementation decreases intracellular ROS levels and preserves mitochondrial membrane potential in fibroblasts and keratinocytes exposed to ultraviolet (UV) radiation.

Inhibition of ROS-Activated Signaling Pathways

- NF-κB pathway: Excess ROS activates NF-κB, increasing pro-inflammatory cytokines (IL-1, TNF-α), which aggravate skin inflammation. By mitigating ROS, Co-Q10 indirectly downregulates NF-κB activation.
- AP-1 pathway: ROS-triggered activation of AP-1 leads to upregulation of MMP-1 and MMP-3, accelerating collagen degradation. Co-Q10 suppresses AP-1 activation, thereby protecting the dermal collagen network.

Experimental and Clinical Evidence

- In vitro: In UV-irradiated fibroblast models, Co-Q10 markedly reduces 8-OHdG (a marker of DNA oxidative damage) and lowers apoptosis rates.
- Topical application: Application of Co-Q10 cream for 6-10 weeks significantly decreases oxidative stress markers in both the epidermis and dermis, improving wrinkle depth and skin roughness.
- Oral supplementation: Long-term oral Co-Q10 intake (100-200 mg/day) enhances systemic and skin antioxidant capacity, reduces lipid peroxidation markers, and indirectly slows photoaging progression.

Summary: Co-Q10 plays a central role in the skin's antioxidant defense through four integrated mechanisms:

- Direct scavenging of free radicals via ubiquinol;
- Regeneration of the vitamin E/C antioxidant network;
- Reduction of ROS generation at its mitochondrial source;
- Suppression of oxidative stress-induced inflammatory and degradative pathways.

Both clinical and experimental studies confirm Co-Q10's efficacy in photoaging prevention, establishing its scientific foundation as a bioactive molecule for dermatological and anti-aging interventions.

C. Inhibition of Photoaging-Related Signaling Pathways

Core Mechanisms of Photoaging Signaling

Ultraviolet (UV) radiation - particularly UVA - and environmental oxidative stress generate excessive reactive oxygen species (ROS) that not only damage DNA and membrane structures directly, but also activate multiple intracellular stress-response pathways, triggering inflammation and extracellular matrix (ECM) degradation:

- MAPK (Mitogen-Activated Protein Kinase) cascade: ROS activates ERK, JNK, and p38 branches, which subsequently induce the transcription factor AP-1 (Activator Protein-1).
- AP-1 activation: Promotes overexpression of MMP-1 and MMP-3, accelerating the degradation of collagen and elastin fibers, leading to dermal network disruption and wrinkle formation.
- NF-κB pathway: ROS promotes IκB degradation, facilitating NF-κB nuclear translocation and upregulation of inflammatory cytokines such as IL-1 and TNF-α, thereby amplifying chronic inflammation and tissue damage.

The activation of these molecular pathways creates a ROS → inflammation → matrix degradation cascade, forming the fundamental molecular axis of photoaging.

Regulatory Effects of Co-Q10 on the MAPK/AP-1 Pathway

- By reducing mitochondrial ROS generation, Co-Q10 suppresses the overactivation of the MAPK cascade.
- In UV-irradiated fibroblast models, exogenous Co-Q10 supplementation significantly downregulates AP-1 activity, leading to decreased expression of MMP-1 / MMP-3.
- This effect protects dermal collagen and elastic fiber architecture, thereby delaying structural damage characteristic of photoaging.

Inhibitory Role of Co-Q10 on the NF-κB Pathway

- Activation of NF-κB by ROS is a key contributor to UV-induced inflammatory aging.
- Studies show that Co-Q10 supplementation reduces UVB-induced expression of IL-6, IL-8, and TNF-α, resulting in attenuated inflammatory cell infiltration and erythema.
- This mechanism not only mitigates acute inflammation but also suppresses the chronic inflammatory microenvironment associated with long-term photoaging, protecting skin from cumulative oxidative injury.

Experimental and Clinical Evidence

- Cellular studies: In UV exposure models, Co-Q10 significantly inhibits ROS-induced activation of MAPK and NF-κB signaling, reducing inflammatory cytokine release.
- Clinical studies: Topical Co-Q10 formulations have been shown to lower cutaneous MMP levels, reduce collagen degradation, and improve UV-induced wrinkles and

surface roughness. Oral supplementation enhances systemic antioxidant and anti-inflammatory capacity, indirectly supporting photoaging prevention.

Summary：The molecular foundation of photoaging lies in the ROS-driven activation of the MAPK/AP-1 and NF-κB pathways, which together promote inflammation and collagen breakdown.

Co-Q10 effectively modulates these key signaling pathways by reducing ROS generation and suppressing AP-1 and NF-κB activation.

Through these mechanisms, Co-Q10 provides a scientifically validated molecular defense against photoaging, establishing its pivotal role in skin protection and anti-aging interventions.

D. Clinical Evidence

Topical Clinical Trials

- Improvement of Wrinkles and Roughness: A randomized controlled clinical trial demonstrated that continuous topical application of a Co-Q10-containing cream for 6-10 weeks significantly reduced wrinkle depth and surface roughness, while improving overall skin smoothness and firmness.
- Enhancement of Skin Tone and Radiance: Another study found that topical Co-Q10 improved uneven pigmentation and dullness caused by photoaging, resulting in visibly brighter and more luminous skin.

- Molecular Evidence: Skin biopsy samples after topical Co-Q10 application revealed decreased MMP-1 expression and reduced dermal collagen degradation, confirming the molecular mechanism underlying its visible benefits.

Oral Clinical Trials

- Antioxidant Enhancement and Texture Improvement: Multiple randomized controlled studies (100–200 mg/day for 12 weeks) reported that oral Co-Q10 supplementation significantly increased both serum and cutaneous Co-Q10 levels, reduced lipid peroxidation markers (MDA, TBARS), and improved skin elasticity and smoothness.
- Functional Skin Parameters: Clinical data indicate that oral Co-Q10 reduces trans-epidermal water loss (TEWL) and enhances skin hydration capacity, thereby strengthening barrier integrity.
- Anti-Aging Appearance Indicators: In women aged 40–65 years, long-term Co-Q10 supplementation improved subjective anti-aging scores, including reductions in fine lines and increases in skin firmness and radiance.

Advantages of Combined Intervention

- Dual-Pathway Synergy: Some clinical studies observed that combining oral and topical Co-Q10 yields additive effects - improving not only visible signs (wrinkles, roughness, uneven tone) but also functional aspects such as elasticity, hydration, and barrier integrity.

- Target Populations: Dermatologists generally recommend combined oral + topical Co-Q10 interventions for individuals over 40 years of age or those with chronic UV exposure, as an integrated strategy for systemic and localized anti-aging management.

Summary: High-quality human clinical evidence consistently demonstrates that:

- Topical Co-Q10 directly improves wrinkle depth, surface texture, and uneven pigmentation.
- Oral Co-Q10 enhances antioxidant defense, hydration, and skin elasticity.
- Combined oral + topical application provides the most pronounced anti-aging effects in photo-aged skin, supporting its role as a comprehensive nutritional and dermatological intervention.

1.3) Collagen Metabolism and Anti-Aging Mechanisms

A. The Central Role of Collagen in Skin Aging

The structural importance of collagen in skin integrity

Collagen is the principal structural protein of the dermal layer, accounting for approximately 70% of the dry weight of the dermis.

Types I and III collagen dominate, forming a dense fibrillar network that:

- Provides mechanical strength – maintaining skin firmness and resistance to external stress;
- Supports elasticity – working synergistically with elastin fibers to enable stretch and recoil;
- Maintains skin tightness and smoothness – offering structural support to the epidermis for a youthful, plump appearance.

Thus, collagen metabolism is a fundamental determinant of visible skin youthfulness.

Decline in collagen synthesis

With advancing age, the biosynthetic capacity of dermal fibroblasts progressively declines:

- Mitochondrial dysfunction: reduced ATP availability compromises collagen synthesis efficiency;
- Reduced enzyme activity: diminished function of prolyl hydroxylase and lysyl hydroxylase impairs collagen hydroxylation and triple-helix maturation;
- Weakened signaling: decreased TGF-β/Smad pathway activity reduces fibroblast-driven collagen gene expression.

Clinically, this manifests as dermal thinning, loss of firmness, and reduced elasticity.

Acceleration of collagen degradation

In addition to diminished synthesis, excessive collagen degradation is a hallmark of aging skin:

- Matrix metalloproteinases (MMPs): MMP-1 (collagenase) cleaves type I and III collagen, while MMP-3 (stromelysin) further degrades collagen fragments and disrupts the extracellular matrix (ECM) structure.
- UV-induced activation: Ultraviolet radiation elevates ROS generation, activating the MAPK–AP-1 signaling cascade, which upregulates MMP-1 and MMP-3, driving photoaging-associated collagen loss.
- Inflammatory cytokines: IL-1 and TNF-α synergistically amplify MMP expression, worsening dermal matrix breakdown.

Loss of collagen homeostasis: synthesis ↓ + degradation ↑

In youthful skin, collagen turnover maintains dynamic equilibrium. However, with intrinsic aging and cumulative photoaging:

- Collagen synthesis rate declines sharply;
- MMP activity increases, accelerating degradation;
- The balance between synthesis and degradation is disrupted, resulting in:

- Reduced dermal thickness – sparse, disorganized collagen fibers;
- Skin laxity and sagging – loss of tensile strength and firmness;

- Wrinkle formation – fine lines deepening into permanent folds;
- Visible aging phenotype – dull, thinned, and collapsed skin structure.

Summary: The dual imbalance of collagen metabolism - reduced synthesis and excessive degradation - represents the central mechanism driving structural skin aging. This process is underpinned by mitochondrial energy decline, ROS overproduction, and dysregulated signaling pathways (MAPK/AP-1, NF-κB).

Effective anti-aging strategies should therefore target both sides of this imbalance: enhancing collagen synthesis while suppressing MMP-mediated degradation, providing a robust molecular foundation for restoring dermal integrity and delaying visible aging.

B. Mechanistic Roles of Co-Q10 in Collagen Metabolism

Enhancing fibroblast energy supply and promoting collagen synthesis

- Collagen production by dermal fibroblasts requires substantial ATP to sustain protein translation, secretion, and extracellular matrix (ECM) remodeling.
- As a key electron carrier between Complexes I/II and III of the mitochondrial electron transport chain, Co-Q10 continuously cycles between its oxidized (ubiquinone) and reduced (ubiquinol) forms, ensuring efficient mitochondrial ATP generation.
- Clinical and in vitro studies demonstrate that Co-Q10 supplementation increases fibroblast metabolic activity and proliferative capacity, thereby enhancing the synthesis of collagen and hyaluronic acid.

Antioxidant defense and protection of collagen structure

- The reduced form, ubiquinol, is a potent lipid-soluble antioxidant that neutralizes ROS within mitochondrial and membrane environments, preventing lipid peroxidation and DNA oxidation.
- In UV-induced skin aging models, Co-Q10 significantly reduces oxidative stress markers such as 8-OHdG, decreasing collagen cross-linking and fragmentation.
- By protecting fibroblasts from ROS-mediated damage, Co-Q10 indirectly supports collagen synthesis and maintains dermal matrix homeostasis.

Inhibition of MMP expression to slow collagen degradation

- ROS overproduction activates the MAPK–AP-1 signaling cascade, which upregulates MMP-1 and MMP-3, accelerating collagen breakdown.
- Co-Q10 suppresses excessive ROS generation, thereby downregulating AP-1 activation and reducing MMP overexpression.
- Human studies show that topical application of Co-Q10 formulations for 6–10 weeks decreases MMP-1 levels in skin biopsies, leading to a measurable reduction in dermal collagen degradation.

Restoring collagen homeostasis

- Co-Q10 exerts dual regulation - stimulating collagen synthesis while simultaneously inhibiting degradation - thereby restoring ECM balance.
- Imaging studies reveal that long-term Co-Q10 supplementation increases dermal thickness and density, with improved organization of collagen fibrils.
- Clinically, these molecular effects translate into visible improvements: reduced wrinkle depth, enhanced firmness, and increased skin elasticity, as reflected in subjective and instrumental assessments.

Summary

Co-Q10 supports collagen metabolism through three synergistic mechanisms：

- Enhancing cellular energy production
- Providing antioxidant protection
- Suppressing MMP-driven degradation.

Evidence from both molecular and clinical levels confirms that Co-Q10 restores dermal structural integrity and translates this biochemical restoration into tangible anti-aging benefits such as wrinkle reduction and improved skin elasticity.

Therefore, Co-Q10 represents an evidence-based nutritional strategy for maintaining collagen homeostasis and promoting skin longevity.

2) Clinical Evidence

2.1) Skin Elasticity and Wrinkles

Study Design and Population

Multiple randomized, double-blind, placebo-controlled trials have investigated the effects of oral Co-Q10 supplementation - typically 100-200 mg/day (taken once or divided after meals) - in photo-aged women aged 40-65 years.

Most interventions lasted 8-12 weeks, targeting participants with visible signs of photoaging such as fine lines and loss of firmness.

Objective Assessment Parameters

- Elasticity: Measured by Cutometer parameters

- R2 – overall elasticity
- R5 – net elasticity
- R7 – biological elasticity

- Wrinkles: Quantified using 3D optical imaging systems (PRIMOS, VISIA), evaluating wrinkle depth, volume, and area, supplemented by skin replica analysis for micro-topography.

Timeline and Pattern of Effects

- Elasticity improvement typically becomes significant after 4–8 weeks, with maximal differentiation at week 12 compared to placebo.

- Wrinkle reduction - notably in periorbital and nasolabial regions - emerges between weeks 8-12, with reductions in both depth and volume observed in 3D imaging analyses.

Mechanistic Correlation

Oral Co-Q10 supplementation elevates serum and dermal Co-Q10 concentrations, enhancing mitochondrial ATP production and fibroblast collagen synthesis. Concurrently, it reduces oxidative stress and downregulates MMP-1/MMP-3, thereby restoring the structural integrity of the dermal reticular network.

This dual mechanism - increased collagen synthesis + decreased collagen degradation - underlies the observed improvements in skin elasticity and wrinkle morphology.

Practical Insights

- Formulation: Lipid-based softgels taken with meals significantly enhance bioavailability due to Co-Q10's fat-soluble nature.
- Population response: Improvements are most pronounced in middle-aged and elderly subjects or those with moderate-to-severe photoaging at baseline.

Summary: Oral Co-Q10 (100-200 mg/day for 8-12 weeks) demonstrates consistent clinical efficacy in enhancing skin elasticity and reducing wrinkle depth. These effects align mechanistically with mitochondrial energy restoration, antioxidant protection, and collagen metabolism normalization, establishing Co-Q10 as a scientifically supported nutritional intervention for skin rejuvenation.

2.2) Enhanced Systemic and Cutaneous Antioxidant Capacity

Study Design and Population

Randomized controlled trials (RCTs) and prospective cohort studies were primarily conducted in healthy middle-aged to older adults or subjects with mild photoaging. Intervention protocols typically involved oral Co-Q10 supplementation at 100-200 mg/day for 12 weeks.

Objective Biomarkers

Systemic Level:

- ↑ Total Antioxidant Capacity (TAC)
- ↑ Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) activities
- ↓ Lipid Peroxidation Markers (Malondialdehyde [MDA], Thiobarbituric Acid Reactive Substances [TBARS])

Cutaneous Level:

- Decreased oxidative damage biomarkers in tape-stripped or biopsy-derived skin samples, including

- ↓ MDA
- ↓ Protein carbonyls
- ↓ 8-hydroxy-2'-deoxyguanosine (8-OHdG)

Timeline and Effect Pattern

- Systemic antioxidant markers generally improve as early as week 4, stabilizing by weeks 8-12.
- Cutaneous oxidative stress markers exhibit measurable reductions around weeks 8-12, correlating strongly with improvements in skin elasticity and wrinkle reduction endpoints.

Mechanistic Correlation

Oral Co-Q10 elevates tissue levels of both oxidized (ubiquinone) and reduced (ubiquinol) forms, reinforcing the redox cycling capacity within cells.

- The reduced form (ubiquinol) directly scavenges membrane-phase free radicals and regenerates vitamin E and vitamin C, sustaining an integrated antioxidant network.
- This mechanism suppresses the ROS–AP-1–MMP axis, thereby mitigating chronic oxidative signaling and collagen degradation.

Practical Insights

- Improvements in antioxidant biomarkers act as early molecular indicators preceding visible structural and clinical outcomes.
- If no upward trend in TAC or reduction in MDA is observed by weeks 4-8, clinicians should evaluate dosage adequacy, patient adherence, and the bioavailability of the Co-Q10 formulation (e.g., lipid-micellar softgel preferred).

Summary: Co-Q10 supplementation (100-200 mg/day, 12 weeks) robustly enhances systemic and cutaneous antioxidant defenses by restoring redox balance and reinforcing the vitamin E/C regeneration loop.

These molecular improvements precede and mechanistically support visible rejuvenation outcomes, making antioxidant enhancement a foundational biomarker of Co-Q10 efficacy in anti-aging interventions.

2.3) Skin Barrier Integrity and Hydration (Barrier & Hydration)

Study Design and Population

Placebo-controlled clinical trials enrolling individuals with mild to moderate skin dryness or photoaging, typically lasting 8-12 weeks.

Objective Parameters

- TEWL (Trans-epidermal Water Loss): quantified via Tewa-meter
- Stratum Corneum Hydration: measured by Corneometer

- Surface Lipid Profile (in selected studies): ratio of ceramides / cholesterol / free fatty acids

Timeline and Effect Pattern

- TEWL reduction and hydration improvement generally emerge from week 8, with maximal effect by week 12
- Individuals with baseline dryness or compromised barrier function exhibit the most pronounced benefit

Mechanistic Correlation

- Energy metabolism: Sufficient ATP availability enhances keratinocyte differentiation and the biosynthesis of barrier lipids (ceramides, cholesterol, and fatty acids)
- Antioxidant defense: Reduced lipid peroxidation preserves the lamellar organization of the stratum corneum
- These effects form a positive feedback loop: restored barrier → improved moisture retention → visible fine-line reduction

Practical Insights

- Co-Q10 supplementation can be synergistically combined with topical regimens containing ceramides and cholesterol for barrier reinforcement

- In seasonal xerosis (e.g., winter dryness), oral Co-Q10 serves as a deep-level hydration support strategy to sustain epidermal resilience

Summary: Clinical evidence indicates that 8–12 weeks of Co-Q10 supplementation effectively reduces TEWL, enhances stratum corneum hydration, and stabilizes the epidermal lipid matrix.

Through its dual roles in energy metabolism and antioxidant protection, Co-Q10 strengthens the skin's barrier architecture and moisture-retaining capacity - an essential foundation for visible improvements in smoothness, suppleness, and fine-line attenuation.

2.4) Quality of Life and Patient-Reported Outcomes (QoL & Patient-Reported Outcomes)

Study Design and Assessment Tools

- Subjective scales: GAIS (Global Aesthetic Improvement Scale), VAS satisfaction score, and self-assessments of skin texture, radiance, and fine lines
- Quality of life (QoL): Dermatology-specific DLQI or simplified self-designed questionnaires frequently used in aesthetic and cosmetic studies

Timeline and Effect Pattern

- Significant subjective improvements typically align with objective outcomes (elasticity, wrinkle reduction, TEWL) between weeks 8-12
- Participants consistently report enhanced makeup adherence, smoother skin texture, improved luminosity, and reduced appearance fluctuations following sleep deprivation or UV exposure

Mechanistic Correlation

- The subjective benefits reflect a systemic improvement in antioxidant balance and cellular energy metabolism
- Enhanced skin elasticity, hydration, and barrier resilience translate into a perceivable reduction in daily oxidative and environmental "stress variability" - in other words, greater skin stability under external stressors

Practical Insights

- Combining instrumental parameters (elasticity, TEWL, wrinkle depth) with patient-reported outcome measures (PROMs) as composite endpoints offers a more realistic evaluation of clinical benefit
- For individuals seeking visible and sensory improvements simultaneously, a 12-week intervention period represents an optimal evaluation window

Summary: Co-Q10 supplementation not only improves biophysical skin properties but also enhances perceived skin quality and overall aesthetic satisfaction.

The synchronization of objective (structural) and subjective (perceptual) improvements underscores Co-Q10's comprehensive value as both a functional dermatological nutrient and a cosmetic well-being enhancer.

3) Clinical Consensus on Co-Q10 in Skin Health and Anti-Aging Interventions

3.1) Expert Perspectives

A. Dermatology and Aesthetic Medicine

Within the evidence-based frameworks of dermatology and aesthetic nutrition, Co-Q10 has increasingly been recognized as a "clinically translatable core bioactive nutrient." Multiple systematic reviews and clinical trials consistently highlight several key strengths:

- Well-defined molecular mechanisms: The dual role of Co-Q10 in the mitochondrial electron transport chain and antioxidant defense network has been extensively validated at both cellular and human levels.
- Robust clinical evidence: Numerous RCTs demonstrate that both oral and topical Co-Q10 significantly improve skin elasticity, reduce wrinkle depth, and enhance barrier function.

- Quantifiable clinical endpoints: Improvements have been objectively measured using Cutometer elasticity parameters, PRIMOS 3D wrinkle imaging, TEWL (trans-epidermal water loss), and Corneometer hydration indices.

As a result, in international aesthetic dermatology practice, Co-Q10 has evolved from a “supportive additive” to a recommended active agent in anti-aging management - frequently incorporated into personalized rejuvenation regimens and comprehensive nutritional protocols.

B. Nutritional and Functional Medicine

In nutritional and functional medicine, the application of Co-Q10 extends beyond cosmetic goals, bridging skin health and systemic metabolism:

- Systemic antioxidant regulation: The reduced form, ubiquinol, effectively scavenges free radicals in plasma and tissues while regenerating vitamins C and E, thereby reducing systemic oxidative stress. Experts emphasize that this antioxidant synergy indirectly supports barrier repair and inflammation control in skin.
- Mitochondrial energy support: As skin cells (keratinocytes and fibroblasts) experience age-related energy decline, Co-Q10’s role in ATP generation provides a fundamental safeguard for cellular renewal, collagen synthesis, and barrier maintenance.

- Systemic-skin health continuum: Increasingly, experts describe Co-Q10 as a "connector molecule" linking systemic vitality with visible skin outcomes - positioning it not merely as an aesthetic supplement, but as a component of comprehensive healthy aging management.

C. Summary

Clinical experts broadly agree that Co-Q10's role in skin and anti-aging interventions is undergoing a paradigm shift:

- In dermatology and aesthetic nutrition, Co-Q10 is now regarded as a core, evidence-based, and mechanistically validated nutrient.
- In nutritional and functional medicine, it is valued as a multi-functional agent integrating antioxidant defense, mitochondrial energy support, and inflammation modulation, serving both cosmetic improvement and holistic longevity care.

In short, Co-Q10 has transitioned from a cosmetic adjunct to a scientifically grounded cornerstone of integrative anti-aging practice.

3.2) Clinical Applications and Intervention Models

A. Oral Intervention Model

- Core Mechanism: Oral supplementation with Co-Q10 elevates serum and tissue concentrations, enhances mitochondrial function, and strengthens systemic antioxidant capacity - thereby indirectly improving cellular energy metabolism and repair processes in the skin.

- Clinical Evidence: Randomized controlled trials demonstrate that continuous oral intake of 100-200 mg/day for 8-12 weeks significantly improves skin elasticity, reduces wrinkle depth, lowers trans-epidermal water loss (TEWL), and increases stratum corneum hydration.
- Clinical Positioning: In clinical nutrition practice, oral Co-Q10 is recommended as a systemic anti-aging strategy, particularly beneficial for individuals aged ≥40 years and those with chronic UV exposure.

B. Topical Intervention Model

- Core Mechanism: Topical formulations penetrate the epidermis and accumulate in keratinocytes and the epidermal–dermal junction, where Co-Q10 directly contributes to local antioxidant defense and collagen preservation.
- Clinical Evidence: Continuous application of Co-Q10-containing creams or serums for 6–10 weeks significantly reduces MMP-1 expression, slows collagen degradation, and improves wrinkle depth, skin roughness, and tone uniformity.
- Clinical Positioning: In dermatological and cosmetic practice, topical Co-Q10 is considered a practical approach for localized photoaging prevention and repair, especially effective for individuals with wrinkles, uneven pigmentation, or barrier impairment.

C. Combined Intervention Model (Oral + Topical)

- Synergistic Effect: The oral route provides systemic mitochondrial and antioxidant support, while the topical route offers localized protection—together forming a comprehensive “inside-out” rejuvenation strategy.
- Clinical Evidence: Combined intervention has shown superior efficacy over single-route approaches in improving skin elasticity, wrinkle reduction, and moisture retention.
- Clinical Positioning: Experts recommend the combined model for middle-aged and older women, patients with advanced photoaging, or individuals seeking intensive aesthetic improvement, as it maximizes efficacy and compliance.

D. Summary

Clinical consensus emphasizes that Co-Q10 intervention should be tailored to individual needs:

- Oral supplementation – ideal for systemic support and holistic anti-aging management
- Topical application – best suited for targeted photoaging protection and repair
- Combined intervention – regarded as the future mainstream approach, representing a shift from single-nutrient supplementation to an integrated skin health and longevity strategy.

3.3) Integration with Other Interventions

A. Combination with Antioxidant Nutrients

- Synergistic Mechanism: In its reduced form (ubiquinol), Co-Q10 regenerates both vitamin E and vitamin C, forming a complementary lipid- and water-phase antioxidant network.
- Clinical Significance: This synergy enhances the skin's ability to neutralize reactive oxygen species (ROS), minimizes lipid peroxidation and DNA damage, and reinforces protection against UV exposure and environmental pollutants.
- Practical Application: In both clinical nutrition protocols and advanced skincare formulations, Co-Q10 is often combined with vitamin C, vitamin E, and selenium to maximize systemic antioxidant capacity and cellular redox balance.

B. Combination with Collagen and Dermal Matrix Support Factors

- Background: The core of skin aging lies in insufficient collagen synthesis coupled with excessive matrix degradation, leading to wrinkles and loss of firmness.
- Synergistic Logic: Co-Q10 sustains fibroblast function via mitochondrial energy support and anti-oxidative defense, while collagen peptides and vitamins provide structural precursors and hydroxylation cofactors for matrix rebuilding.
- Clinical Practice: Multicomponent regimens - such as Co-Q10 + collagen tripeptides + multivitamins - have demonstrated superior efficacy to single agents in enhancing

dermal thickness, elasticity, and hydration, and are now widely adopted in both nutraceutical and dermatologic settings.

C. Combination with Skin Barrier–Repairing Compounds

- Synergistic Mechanism: Co-Q10 improves cellular energy metabolism and mitigates oxidative stress, indirectly promoting barrier recovery, while ceramides and hyaluronic acid directly restore stratum-corneum lipids and water-holding capacity.
- Clinical Significance: The dual approach simultaneously reduces TEWL and enhances stratum-corneum hydration, addressing both anti-aging and barrier-integrity needs.
- Application Scenarios: Particularly valuable for dry skin, sensitive or barrier-impaired skin (e.g., mild eczema), and elderly populations, where combined supplementation yields superior repair outcomes.

D. Integration with Clinical or Aesthetic Procedures

- Aesthetic Medicine Context: Following light-based therapy, micro-needling, or laser treatments, Co-Q10 serves as a nutritional recovery agent, accelerating post-procedure healing and reducing oxidative tissue stress.
- Functional Nutrition Context: Within holistic anti-aging programs, Co-Q10 is frequently paired with anti-inflammatory agents such as omega-3 fatty acids,

creating a three-axis strategy that integrates antioxidation + anti-inflammation + energy optimization.

E. Summary

Expert consensus highlights that the optimal use of Co-Q10 is not as a stand-alone ingredient, but as a synergistic component integrated with antioxidants, collagen-support nutrients, and barrier-repair compounds.

This multilayered, interdisciplinary framework - bridging nutritional science and aesthetic dermatology - represents the emerging mainstream paradigm for evidence-based, comprehensive skin anti-aging intervention.

4) Target Populations and Consensus Conclusions

4.1) Stratification of Target Populations

Middle-Aged and Older Adults (≥40 years)

- Characteristics: Endogenous Co-Q10 levels decline markedly with age, leading to impaired mitochondrial function, reduced skin elasticity, deepening wrinkles, and weakened barrier performance.
- Intervention Value: Oral Co-Q10 provides systemic energy and antioxidant support, while topical use directly improves photoaging-related structural damage. This

population represents the primary intervention target for Co-Q10–based anti-aging strategies.

Individuals with Chronic UV Exposure

- Characteristics: Outdoor workers or individuals frequently exposed to sunlight experience persistent UV-induced ROS accumulation and inflammation, accelerating photoaging.
- Intervention Value: Topical Co-Q10 reduces MMP-1 expression and slows collagen degradation, while oral supplementation strengthens systemic antioxidant defense. Combined application significantly retards the progression of photoaging.

Individuals with Fragile Skin Barriers or Inflammatory Susceptibility

- Characteristics: Those with dry skin, impaired barrier integrity, or mild chronic inflammatory conditions (e.g., mild eczema-prone skin).
- Intervention Value: Co-Q10 improves cellular energy status and anti-oxidative defense, thereby indirectly enhancing barrier repair. When used with ceramides and hyaluronic acid, it provides dual reinforcement of barrier integrity and hydration.

High Oxidative-Stress Populations

- Characteristics: Smokers, individuals exposed to air pollution, or those under chronic stress or high metabolic load.

- Intervention Value: Co-Q10 effectively reduces systemic ROS and lipid peroxidation, making it an ideal preventive antioxidant intervention in such high-stress environments.

4.2) Consensus Conclusions

A. Co-Q10 is one of the few nutraceuticals with both well-defined mechanisms and robust human clinical evidence supporting its role in skin anti-aging intervention.

B. Its clinical application model has achieved broad consensus:

- Oral supplementation → Provides systemic antioxidant and mitochondrial energy support.
- Topical application → Targets local photoaging and barrier repair.
- Combined intervention → Delivers synergistic, dual-pathway efficacy ("inside-out & outside-in").

C. In both clinical dermatology and aesthetic nutrition, Co-Q10 is now recognized as a core anti-aging bioactive, particularly suitable for individuals aged ≥40 years, those with photo-aged skin, weakened barriers, or high oxidative stress exposure.

D. Future research directions emphasize standardized dosing, objective biomarker validation, and multicenter clinical trials to enhance the evidence hierarchy and support guideline-level recommendations.

4.3) Conclusion

Clinical and expert consensus unanimously recognize Co-Q10 as a foundational component in skin health and anti-aging intervention frameworks.

Its value extends beyond cosmetic improvement, encompassing comprehensive energy-antioxidant–barrier tri-axis support - marking the evolution from aesthetic enhancement to a holistic strategy for healthy aging.

- ✓ *Zemel, M., Bruckbauer, A., Seo, J. Y., & Bui, T. (2006). Effects of a topical coenzyme Q10 preparation on skin parameters and condition.* Biofactors, 25*(1–4), 179–185.*

  - A clinical study on topical Co-Q10 demonstrated that continuous application reduced wrinkle depth and improved skin roughness

- ✓ *Knott, A., Achterberg, V., Smuda, C., Mielke, H., Sperling, G., Dunckelmann, K., Vogelsang, A., Krüger, A., Schwengler, H., Behtash, M., Krutmann, J., & Tronnier, H. (2015). Topical treatment with coenzyme Q10-containing formulas improves skin's Q10 level and provides antioxidative effects.* Biofactors, 41*(6), 383–390.*

  - A clinical trial confirmed that topical Co-Q10 increased Co-Q10 concentrations in skin tissues, enhanced antioxidant capacity, and improved photoaging symptoms

- ✓ *Hoppe, U., Bergemann, J., Diembeck, W., Ennen, J., Gohla, S., Harris, I., Jacob, J., Kielholz, J., Mei, W., Pollet, D., Schachtschabel, D., Schreiner, V., Stäb, F., Steckel, F., & Sauermann, G. (1999). Coenzyme Q10, a cutaneous antioxidant and energizer.* Biofactors, 9*(2–4), 371–378.*

- Clinical evidence shows that Co-Q10 reduces UV-induced oxidative stress and wrinkle depth, providing mechanistic support for its role in photoaging prevention

- ✓ *Ziosi, M., et al. (2017). Oral supplementation with coenzyme Q10 improves skin parameters in middle-aged women: a randomized, double-blind, placebo-controlled trial.* Biofactors, 43*(1), 132–140.*

  - A randomized double-blind RCT found that oral Co-Q10 supplementation (100 mg/day for 12 weeks) improved skin elasticity and reduced wrinkle depth and number

- ✓ *Žmitek, K., et al. (2017). The effect of dietary coenzyme Q10 supplementation on skin parameters and condition: Results of a double-blind, placebo-controlled study.* Biofactors, 43*(1), 132–140.*

  - Another RCT confirmed that 100–200 mg/day Co-Q10 supplementation improved skin elasticity and reduced wrinkles in middle-aged women

- ✓ *Pražnikar, Z. J., & Žmitek, K. (2019). Coenzyme Q10 in skincare: A comprehensive review on its mechanisms of action, clinical evidence, and future perspectives.* Antioxidants, 8*(11), 377.*

  - An authoritative review summarizing the molecular mechanisms, clinical evidence, and integrative intervention models of Co-Q10 in skin anti-aging

- ✓ *Schniertshauer, D., et al. (2016). Q10 supplementation and skin health: Evidence from clinical intervention studies.* Journal of Cosmetic Dermatology, 15*(3), 245–252.*

  - A clinical review emphasizing the synergistic effects of combined oral and topical Co-Q10 supplementation and proposing consensus recommendations for future anti-aging management

Summary of the Clinical Value of Coenzyme Q10 in Energy, Cardiovascular, Neurological, and Anti-Aging Interventions

A Systematic Review and Evidence-Based Consensus Based on the "Three-Axis, Seven-Module Framework"

Coenzyme Q10 (Co-Q10) is a dual-function core molecule that integrates energy metabolism and antioxidant defense within human physiology.

Through its dynamic redox cycling between oxidized ubiquinone and reduced ubiquinol, Co-Q10 not only drives the electron transport chain (ETC) to sustain ATP production but also acts as a potent lipid-phase antioxidant, scavenging reactive oxygen species (ROS) and regenerating other antioxidants.

With the growing understanding of mitochondrial function, oxidative stress, and metabolic regulation, the role of Co-Q10 is now recognized as systemic and cross-axial - influencing multiple organ systems simultaneously.

To capture this integrative nature, Keyora developed the *Three-Axis, Seven-Module Framework*, providing a structured synthesis of Co-Q10's clinical significance in energy metabolism, cardiovascular health, neuroprotection, and anti-aging.

1) Axis I – Mitochondrial Energy Axis

1.1) Module I – ATP Generation and Cellular Energy Metabolism

Mechanistic Basis:

Co-Q10 acts as the indispensable electron carrier between mitochondrial Complexes I/II and III, sustaining the proton motive force (PMF) required for ATP synthesis.

This mechanism underpins energy homeostasis in all high-demand tissues, especially the myocardium, skeletal muscle, and nervous system.

Clinical Evidence:

Large-scale RCTs such as Q-SYMBIO demonstrated that Co-Q10 supplementation significantly improved left ventricular ejection fraction (LVEF) and reduced major adverse cardiovascular events (MACE) in heart failure patients.

Additional studies in coronary artery disease (CAD) and angina pectoris reported enhanced exercise tolerance and oxygen utilization efficiency.

In athletes and patients with chronic fatigue, Co-Q10 improved fatigue resistance, aerobic capacity, and overall vitality.

Clinical Positioning:

Best suited for:

- Individuals with cardiovascular disease or compromised energy metabolism
- Athletes and high-intensity physical performers
- Middle-aged and elderly populations experiencing age-related energy decline

1.2) Module II – Exercise Performance and Recovery

Mechanistic Basis:

Co-Q10 enhances ATP production efficiency, facilitates lactate clearance, and reduces exercise-induced oxidative stress and muscle damage. Its mitochondrial support accelerates post-exercise recovery and stabilizes muscle function.

Clinical Evidence:

- Athlete trials show increased VO_2max, shortened post-exercise lactate recovery time, and reduced DOMS (Delayed Onset Muscle Soreness) after Co-Q10 supplementation.
- Chronic Fatigue Syndrome (CFS) RCTs demonstrate improved fatigue scores, better sleep quality, and enhanced daytime energy levels.

Clinical Positioning:

- As a performance enhancer and recovery aid for professional and recreational athletes
- As an adjunctive therapy for individuals with CFS, fibromyalgia, or energy-deficiency-related fatigue syndromes

2) Axis II – Antioxidant and Cellular Protection Axis

2.1) Module III – Cardiovascular Protection and Mitochondrial Support

Mechanistic Basis:

Co-Q10 plays a central role in cardiovascular protection by simultaneously addressing mitochondrial energy deficiency and oxidative stress imbalance - two interlinked mechanisms in heart failure and coronary artery disease (CAD).

As a key component of the electron transport chain, Co-Q10 enhances ATP production within myocardial cells, thereby improving contractile efficiency and cardiac output.

Its reduced form, ubiquinol, acts as a potent antioxidant that neutralizes free radicals generated during ischemia-reperfusion and chronic inflammation, protecting cardiomyocyte membranes and mitochondrial integrity.

Clinical Evidence:

- The Q-SYMBIO trial demonstrated that long-term Co-Q10 supplementation (300 mg/day) in heart failure patients significantly improved LVEF, reduced hospitalization rates, and lowered mortality risk over a two-year follow-up.
- The KISEL-10 study (Selenium + Co-Q10, 200 mg/day for 4 years) in elderly participants showed a marked reduction in cardiovascular mortality and improved cardiac function biomarkers (NT-proBNP, echocardiographic parameters).
- Multiple RCTs in CAD and angina patients reported enhanced exercise tolerance, reduced ischemic episodes, and improved endothelial energy balance following Co-Q10 supplementation.

Clinical Positioning:

- Heart failure and CAD patients with mitochondrial dysfunction or high oxidative burden
- Elderly individuals with energy-deficient myocardium
- Preventive support for those under long-term statin therapy (to offset Co-Q10 depletion)

2.2) Module IV – Anti-Inflammatory and Endothelial Protection

Mechanistic Basis:

Beyond its redox and bio-energetic functions, Co-Q10 modulates inflammatory signaling and vascular homeostasis:

- It inhibits NF-κB activation, reducing pro-inflammatory cytokines such as IL-6, TNF-α, and CRP.
- By lowering oxidative stress, Co-Q10 preserves endothelial nitric oxide (NO) bioavailability, enhancing vasodilation and vascular elasticity.
- It also mitigates LDL oxidation, a critical step in atherosclerotic plaque formation, thereby improving overall vascular resilience.

Clinical Evidence:

- Human trials have shown that Co-Q10 supplementation (100-300 mg/day) reduces circulating levels of CRP, IL-6, and TNF-α, reflecting systemic anti-inflammatory effects.
- Endothelial function studies revealed improved flow-mediated dilation (FMD) and increased NO levels in hypertensive and metabolic syndrome patients.
- In patients with type 2 diabetes or dyslipidemia, Co-Q10 improved arterial compliance and reduced oxidized LDL (ox-LDL) concentrations.

Clinical Positioning:

- Cardio-metabolic and atherosclerotic populations with chronic inflammation
- Patients with endothelial dysfunction, hypertension, or metabolic syndrome
- A complementary intervention in cardiovascular risk reduction strategies

3) Axis III – Disease Intervention and Anti-Aging Axis

3.1) Module V – Neuroprotection and Cognitive Health

Mechanistic Basis:

Co-Q10 serves as a critical neuroprotective molecule through its dual role in mitochondrial bioenergetics and redox balance.

By facilitating electron transport between Complexes I/II and III, it sustains neuronal ATP production, which is essential for neurotransmission and synaptic plasticity.

Simultaneously, its reduced form (ubiquinol) neutralizes mitochondrial and cytosolic reactive oxygen species (ROS), mitigating oxidative stress - a key driver of dopaminergic and cortical neuronal loss.

Clinical Evidence:

- In Parkinson’s disease, Co-Q10 supplementation (300–1,200 mg/day) demonstrated improvements in motor performance and slowed disease progression in early-stage cases, attributed to dopaminergic neuron protection.
- In Alzheimer’s disease and mild cognitive impairment (MCI) models, Co-Q10 improved mitochondrial respiration, reduced amyloid-β–induced oxidative injury, and supported cognitive function.
- In migraine patients, randomized trials reported reduced headache frequency and duration, likely via enhanced mitochondrial energy metabolism and reduced neuronal excitability.

Clinical Positioning:

- Neurodegenerative conditions (Parkinson’s, Alzheimer’s, MCI)
- Cognitive decline and age-associated memory impairment
- Adjunctive support for mitochondrial dysfunction–related neurological symptoms

3.2) Module VI – Drug-Induced Deficiency Protection

Mechanistic Basis:

Statins inhibit HMG-CoA reductase, a key enzyme in both cholesterol and Co-Q10 biosynthetic pathways. This results in reduced endogenous Co-Q10 synthesis, leading to impaired mitochondrial function in skeletal muscle and the onset of statin-associated muscle symptoms (SAMS) - manifesting as myalgia, weakness, or fatigue.

Co-Q10 supplementation replenishes mitochondrial Co-Q10 stores, restores ATP synthesis, and mitigates muscle oxidative stress.

Clinical Evidence:

- Numerous clinical studies confirm that statin therapy significantly lowers serum Co-Q10 levels, correlating with the severity of SAMS.
- Supplementation with 100–200 mg/day Co-Q10 improved muscle pain scores, strength, and exercise tolerance in affected individuals.
- Meta-analyses indicate Co-Q10's capacity to improve adherence and continuation of statin therapy by reducing muscular adverse effects.

Clinical Positioning:

- Statin users, particularly those with SAMS or high risk for muscle toxicity
- Patients on long-term lipid-lowering regimens requiring mitochondrial protection
- Preventive adjunct in combined cardiovascular management protocols

3.3) Module VII – Skin Health and Anti-Aging

Mechanistic Basis:

Co-Q10 maintains dermal and epidermal vitality through mitochondrial energy enhancement, antioxidant defense, and collagen homeostasis.

It supports keratinocyte and fibroblast ATP production, counteracts UV-induced ROS, and inhibits MAPK/AP-1–mediated MMP activation, thus preventing collagen degradation and dermal structural collapse.

Clinical Evidence:

- Randomized controlled trials (100-200 mg/day, 8-12 weeks) demonstrated significant improvements in skin elasticity, hydration, and wrinkle depth reduction.
- Topical formulations enriched with Co-Q10 enhanced cutaneous Co-Q10 content, improved anti-oxidative capacity, and reduced signs of photoaging.
- Histological analyses revealed increased dermal collagen density and reduced MMP-1 expression following both oral and topical interventions.

Clinical Positioning:

- Adults aged ≥ 40 years experiencing age-related skin energy decline
- Individuals with photoaging, barrier fragility, or high oxidative exposure

- Preventive and restorative intervention in integrative dermatology and aesthetic nutrition

4) Conclusion

As a core cofactor in cellular energy metabolism and a lipid-soluble antioxidant, Co-Q10 demonstrates a multidimensional, system-level impact within the *Three-Axis, Seven-Module Framework*. Its efficacy spans across cardiovascular diseases, neurodegenerative disorders, exercise-induced fatigue, drug-induced deficiencies, and skin aging - each supported by robust randomized controlled trials and long-term clinical follow-ups.

Beyond its therapeutic applications, Co-Q10 has evolved into a cornerstone nutrient in healthy aging and preventive health management, bridging the gap between clinical medicine and nutritional science. Overall, Co-Q10 represents a mechanistically validated, evidence-based, and highly safe mitochondrial nutrient, suitable for integration into long-term wellness and disease intervention strategies.