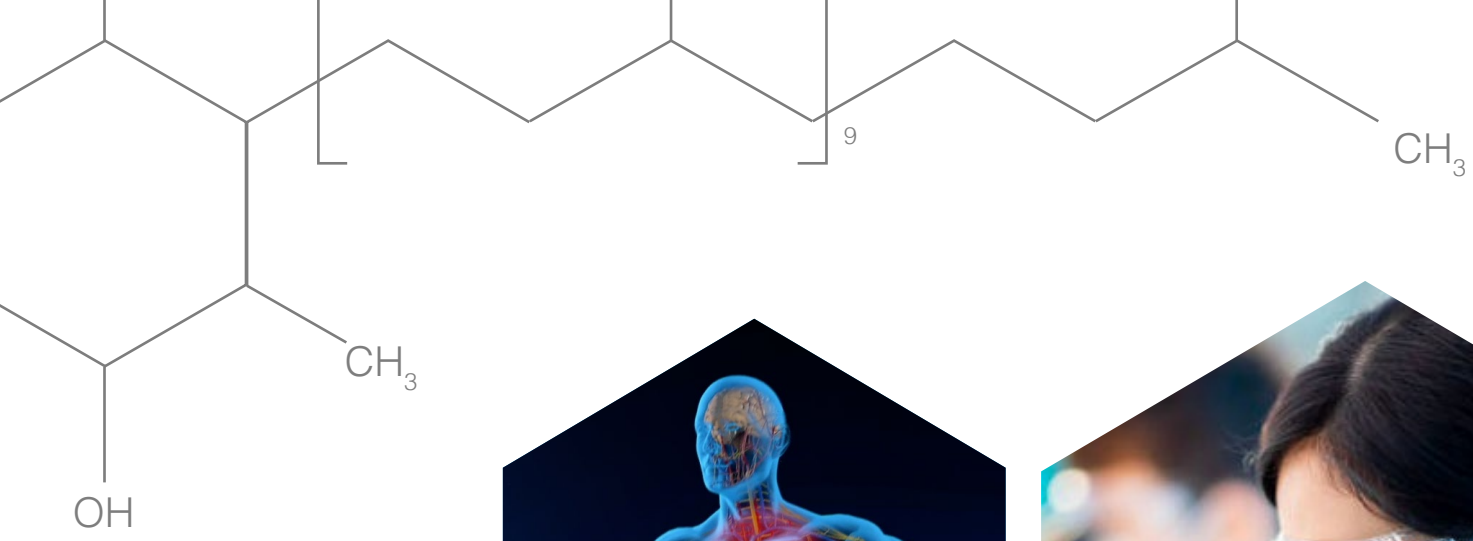
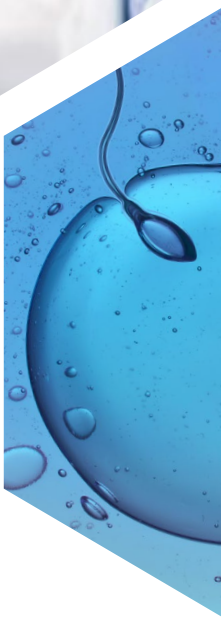
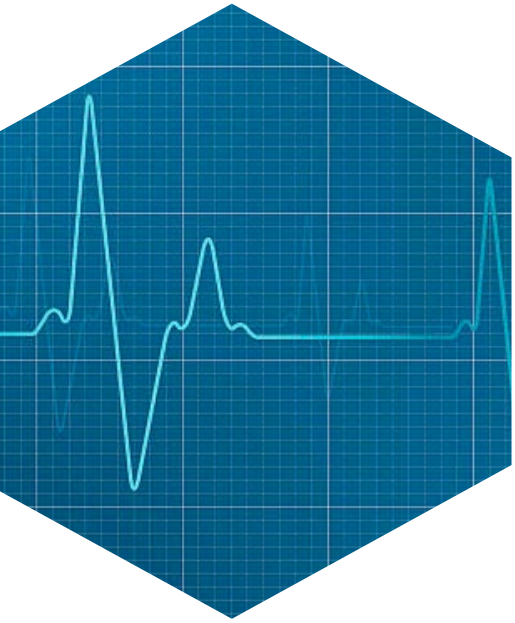


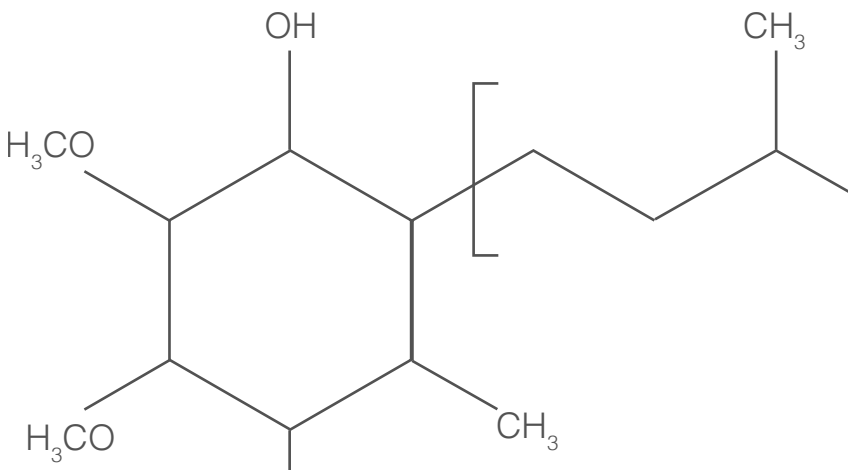
WHITE PAPER SEPTEMBER 2022

MITOCHONDRIAL ENERGY

THE NEW FRONTIER OF HEALTHCARE – ESSENTIAL FOR LIFE & OPTIMAL HEALTH







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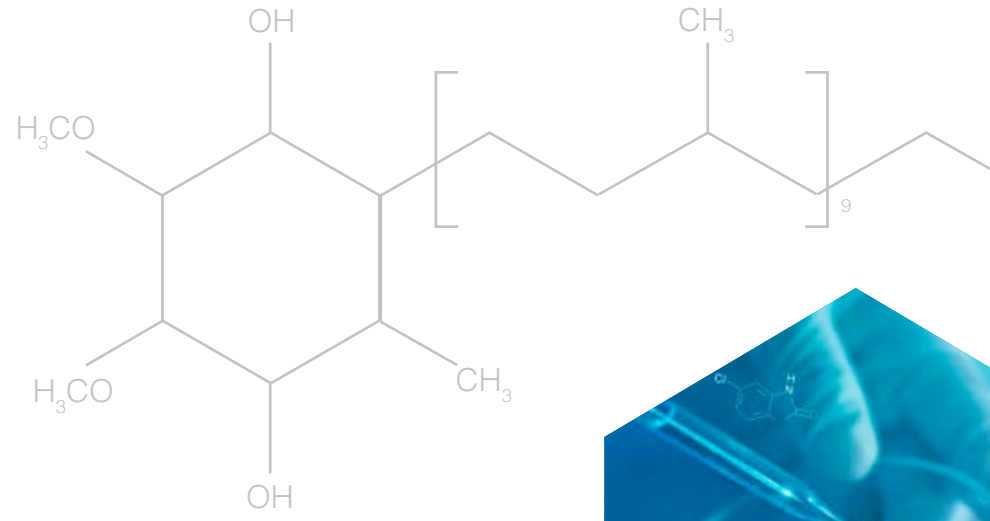


CONTENTS

1

MITOCHONDRIAL ENERGY – THE NEW FRONTIER OF HEALTH

A step towards mitochondria-based therapeutic strategies for optimal health and better patient care

With tremendous progress being made in understanding mitochondrial structure, function and physiology, the role of mitochondria in human health and disease has emerged at the forefront of healthcare in the 21st century.[1] With evidence now unequivocally demonstrating the critical importance of mitochondrial function for optimal health across the lifespan, it is no wonder that scientists are devoting considerable time, money, and effort to further improving our understanding of the many diverse roles that mitochondria play.

Unfortunately, research shows that mitochondrial dysfunction is surprisingly common and associated with most chronic disease states.[2] A change of paradigm seems necessary if we are to have any chance of improving the effectiveness of treatments targeting chronic diseases and, as science rapidly evolves, it is clear that this should include mitochondria-based medicine.[3]

An understanding of chronic disease requires knowledge about mitochondria for diagnostic and therapeutic purposes, with recent research suggesting that restoration of mitochondrial function via a variety of different diet and lifestyle factors, including targeted ubiquinol supplementation, can delay the onset and slow the progression of chronic disease development.[3,4] It is for this reason that the development of key mitochondria-targeted therapeutic strategies has become the new frontier.

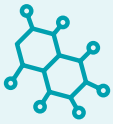
The functional role of mitochondria

Mitochondria are complex cellular organelles governing many diverse yet interconnected metabolic processes in the body.[5] With the exception of red blood cells, all cells in the body contain hundreds to several thousand mitochondria, the number depending on the physiological role and energy needs of the cell.[2]

The primary function of mitochondria is to supply cellular energy by producing adenosine triphosphate (ATP) via the process of oxidative phosphorylation.[6] For this to occur, tricarboxylic acid cycle (TCA) enzymes present in the mitochondrial matrix generate electron carriers that donate electrons to the inner membrane electron transport chain (ETC), the most important part of the ATP creation pathway. The ETC consists of four respiratory enzyme complexes (Complex I, II, III and IV) which work together to generate a number of sequential redox reactions, the ultimate result of which is the phosphorylation of adenosine diphosphate (ADP) to ATP and the release of energy.[7]

The role of mitochondria in human health and disease has emerged at the forefront of healthcare in the 21st century.

It is estimated that the average cell uses 10 billion ATP per day,[2] with mitochondria producing approximately 90% of the biochemical energy that cells need to survive.[8] As ATP cannot be stored, mitochondria must function constantly in order to produce the large amounts of ATP required to sustain life. Ubiquinol is a critical cofactor in the electron transport chain and vital for the generation of ATP.



Ubiquinol is the active and bioavailable form of coenzyme Q10 (CoQ10), while other forms of CoQ10, such as ubiquinone, need to be converted to ubiquinol prior to utilisation by the body. Ubiquinol is naturally present in the body, with around 95% of plasma CoQ10 in the form of ubiquinol.[9]

What's draining our energy?

Eating our way to mitochondrial dysfunction

Several nutrients are essential for mitochondrial functioning, either by acting as cofactors in energy metabolism and/or by acting as antioxidants. As such, diet has a major impact on mitochondrial function.[10] For this reason, there is a potential opportunity for mitochondria to be a target for the prevention/treatment of lifestyle diseases through the manipulation of diet and the prescription of targeted supplementation.

Obesity is a major global health problem and known to be a major risk factor in the development of many metabolic disorders such as diabetes, insulin resistance and cardiovascular disease. While genetic and environmental factors play a role in the development of obesity, studies also demonstrate the role of mitochondrial dysfunction.[1] Obesity leads to various changes in the body, including an increase in inflammatory markers. This is believed to result from excess nutrient supply, which can overwhelm the mitochondrial respiratory chain, leading to an increase in the production of reactive oxygen species, increased oxidative stress and ultimately, mitochondrial dysfunction.[11]

Reduced levels of ubiquinol have been reported in obese individuals,[12] and recent evidence suggests that ubiquinol supplementation may be useful for the treatment of obesity due to its beneficial role in reducing oxidative stress and the inflammatory processes seen in obesity.[13]

Energy concerns with purely plant-based diets

While studies have linked vegetarian diets with improved health outcomes, it still remains unclear whether vegetarian diets ultimately promote longevity and lower the incidence of chronic disease due to the heterogeneous dietary habits of this group.[14] The richest dietary sources of CoQ10 are meat and fish, with lower levels being present in certain oils, vegetables, fruits, and cereals. In comparing plasma CoQ10 levels in healthy vegetarians and vegans with omnivores, the vegetarian/vegan group was found to have significantly lower plasma concentrations of ubiquinol. Due to the essential nature ubiquinol plays in mitochondrial energy production, lower plasma ubiquinol levels may predict an increased risk in age-related diseases in those adhering strictly to a plant-based diet.[14]

Increased stress requires increased energy

There's no doubt about it, we live in a stressful world. Yet something that is not often thought about is that every aspect of the stress response requires energy: energy-dependent enzymatic reactions, sympathetic activation, the synthesis of stress hormones, the release and reuptake of neurotransmitters, behavioural adaptations, and long-term structural remodelling of organs and tissues.[15]

Research has shown that mitochondrial dysfunction, with a subsequent reduction in mitochondrial energy production, compromises the body's ability to respond effectively to stress.[16] As all physiological processes triggered by the stress response are driven by, and highly dependent on, mitochondrial energy production, and at levels exceeding the requirements to sustain basic biological functions, the more stressed we are, the more energy we need to survive.[15] Individuals with higher stress may therefore be more responsive to ubiquinol supplementation.[17,18]

Inflammation and oxidative stress – a dangerous duo

The inflammation triggered by oxidative stress is the cause of many chronic diseases.[19] Oxidative stress is a complex mechanism characterised by an imbalance in the production of reactive oxygen species relative to their elimination by protective mechanisms, resulting in damage to the mitochondrial respiratory chain and ultimately, reduced mitochondrial energy production.[20] While low-to-moderate concentrations of inflammation and oxidative stress are required for cells to maintain healthy conditions, increasing evidence is now emerging for the role of oxidative stress in the onset and/or progression of chronic and degenerative diseases.[21] For this reason, oxidative stress has gathered interest as a therapeutic target.[22]

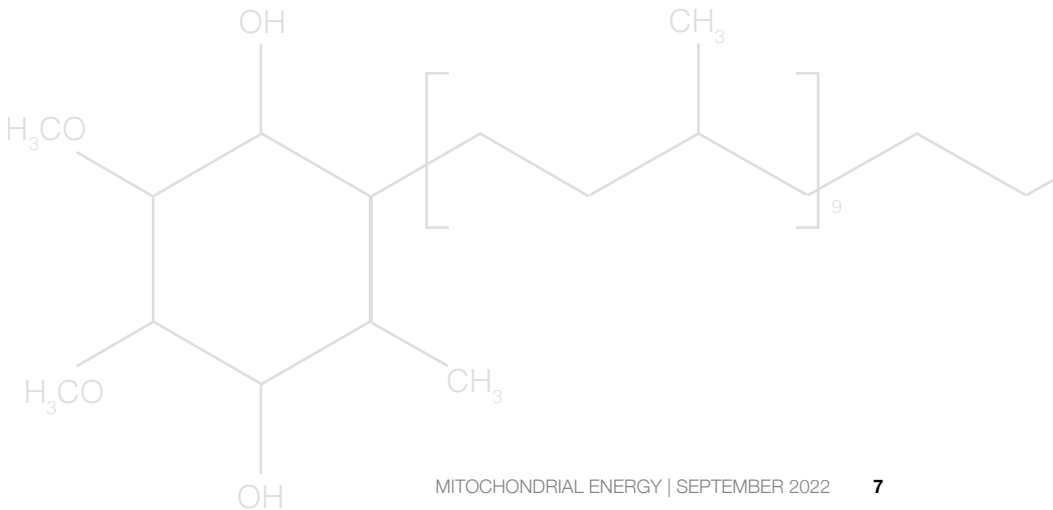
Exogenous antioxidants, as a class of compounds able to counteract oxidative stress and mitigate its negative effects on health, have gained enormous attention in recent times because of the degree of efficacy demonstrated in terms of disease prevention and/or treatment.[23] As an antioxidant, ubiquinol has proved to be of potential use as a treatment in diseases in which oxidative stress is a hallmark.[22]

Providing the right fuel

The ability of mitochondria to produce high-energy molecules such as ATP is directly related to the availability of essential nutrient cofactors.[10] Therapeutic interventions aiming to restore mitochondrial function and optimise ATP production must therefore address an individual's nutrient status via diet and targeted supplementation. While several nutrients are involved in energy generation, helping to produce molecules for the ETC, ubiquinol plays a central and fundamental role.

Table 1. The role of key ETC nutrients required for ATP generation.

NUTRIENT	RELEVANT FUNCTIONS
Ubiquinol	Potent lipid-soluble antioxidant. Plays a critical role in the function of complexes I and II.
Riboflavin	Required for citric acid cycle, and complexes I and II.
Niacin	The precursor of NAD+.
Pantothenic acid	The precursor of CoA.
Vitamin E	Supports complexes I, II and III activities.
Selenium	Required for complexes I and IV.
Taurine	Required for mitochondrial protein translation.



Why are mitochondrial function and ubiquinol status important?

There is no life without energy. Mitochondria have evolved to be the energy factories of our cells, with ubiquinol playing an essential role in this ability to generate ATP.

Since mitochondrial function and behaviour are central to human physiology, it stands to reason that mitochondrial dysfunction is involved in a diverse number of metabolic conditions. Indeed, compromised mitochondrial function is now seen as one of the leading causes of a wide range of disease states including diabetes, obesity, non-alcoholic fatty liver disease, infertility, chronic fatigue syndrome, hypertension, cardiovascular disease, dyslipidaemia, cancer, neurodegenerative diseases and even the aging process itself.[1, 24-28]
In addition to the significant role played in energy production, mitochondria also play essential roles in cell signalling, cellular differentiation, cell growth and cell death, and immune function.[10]

Studies demonstrate that a defect in mitochondrial function in one tissue has consequences for the whole body.[25]
Mitochondrial function can be impaired in several key ways, including:[1, 29]

- Suboptimal ubiquinol levels
- Reduced oxidative phosphorylation
- Decreased ATP production
- The enhanced generation of reactive oxygen species

Under normal physiological conditions, mitochondrial reactive oxygen species (ROS) production and detoxification are tightly balanced. However, oxidative stress occurs when mitochondrial ROS production significantly surpasses the capacity of the cellular antioxidant systems, resulting in damage to cellular components and potentially, cell death.[10] Antioxidants such as ubiquinol, selenium, and vitamins C and E have the ability to reduce oxidative stress, thereby limiting damage to mitochondrial components and the subsequent depletion of mitochondrial energy.

Mechanisms by which antioxidants such as ubiquinol support mitochondrial energy include:[30]

- *Scavenging free radicals*
- *Sequestration of transition metal ions into complexes*
- *Repairing damaged molecules*
- *Breaking chain reactions initiated by free radicals, as in lipid peroxidation*

In 2016, the World Health Organization reported that six of the top ten causes of death worldwide were non-communicable chronic diseases (NCD).[31] Given that both oxidative stress and inflammation have the ability to either damage mitochondria or interfere with mitochondrial repair, it has been suggested that mitochondria may play a principal role in the pathophysiology of NCDs and the growing economic burden that these diseases have on health systems worldwide.[31-33] Prevention of development of mitochondrial NCDs by ubiquinol is one of the basic forms of protection of human health.[34]

It has been suggested that mitochondria may play a principal role in the pathophysiology of NCDs and the growing economic burden that these diseases have on health systems worldwide.[31-33]

2

UBIQUINOL – THE BODY'S SPARK PLUG

Bioenergetics is the study of energy in the human body.[35] It is becoming increasingly clear that problems with energy production are at the heart of many diseases in which mitochondria play a central role.[36] While scientists know a great deal about our primary energy-carrying molecule, ATP, there seems to be a general lack of understanding by healthcare practitioners about how to support mitochondrial bioenergetics in clinical practice.[24] **Also, while the field of mitochondrial medicine is a constantly evolving body of knowledge, ubiquinol's role in mitochondrial bioenergetics is well established.[37]**

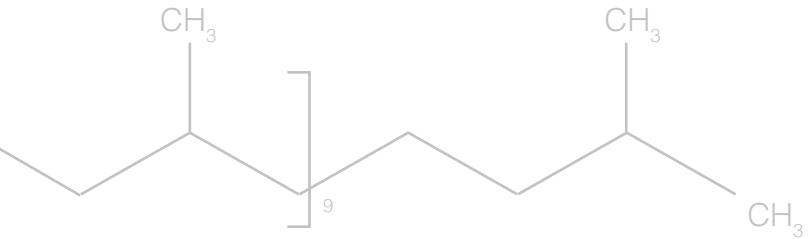
Ubiquinol is a critical cofactor in the electron transport chain, vital for the generation of ATP, the body's essential cellular energy source. As most cellular functions are dependent on an adequate supply of ATP, ubiquinol is essential for the health of virtually all human tissues and organs.[38] In view of this central role of ubiquinol in mitochondrial bioenergetics, it is unsurprising that a ubiquinol depletion has a significant impact on systemic metabolic regulation, neurogenesis, brain function, the regulation of inflammatory pathways, immunity, aging and life-span, and is linked to the pathogenesis of a range of disorders.[4, 22,39-43]

Due to its essential role in energy production, ubiquinol is concentrated in organs that require the most energy, such as the heart, liver, intestines, muscles and kidneys. Ubiquinol accounts for 96% of the total CoQ10 pool in human plasma.[9, 44]

How does ubiquinol work in the body?

Ubiquinol is one of two forms of coenzyme Q10 (CoQ10) naturally found in the body, the other being ubiquinone. CoQ10 is an endogenous lipophilic quinone, found in abundance in the phospholipid bilayer of the inner membrane of the mitochondria present in virtually every human cell, where it acts as a cofactor of mitochondrial respiratory complexes supporting cellular bioenergetics via the production of adenosine triphosphate (ATP).[45] CoQ10 synthesized in the body is ubiquinol.[124] The biosynthesis of ubiquinol is a 17-step complex process requiring at least 11 genes, 8 vitamins and several minerals.[22,46]

Ubiquinol is the reduced and more bioavailable form of CoQ10, named after its ubiquitous nature in the body.[47,48] Ubiquinol comprises a benzoquinone ring conjugated to a ten-unit long isoprenoid chain, giving it increased polarity and bioavailability compared to ubiquinone.[49] The body must first reduce ubiquinone to ubiquinol for it to function. Without this conversion, the body's energy production process cannot be completed and energy levels cannot be sustained.[50]

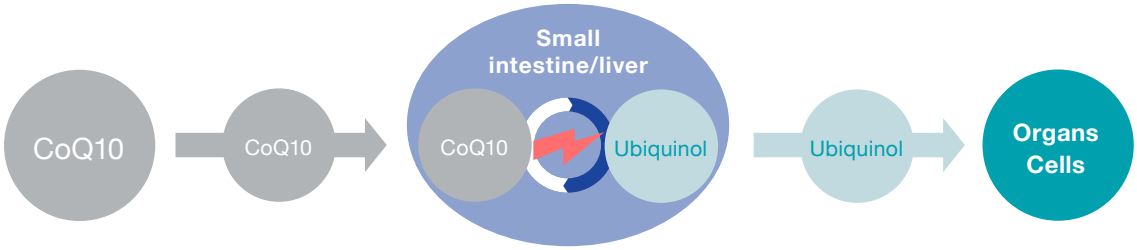


In the mitochondrial respiratory chain, CoQ10 is responsible for electron transport from protein complex I to protein complex II, and from complex II to complex III. When receiving the electrons from both complex I and complex II, it remains in its reduced form as ubiquinol and, after transferring the electrons to complex III, it returns to its oxidized form as ubiquinone.[51]

Uptake of ubiquinol versus conventional CoQ10 in the body.

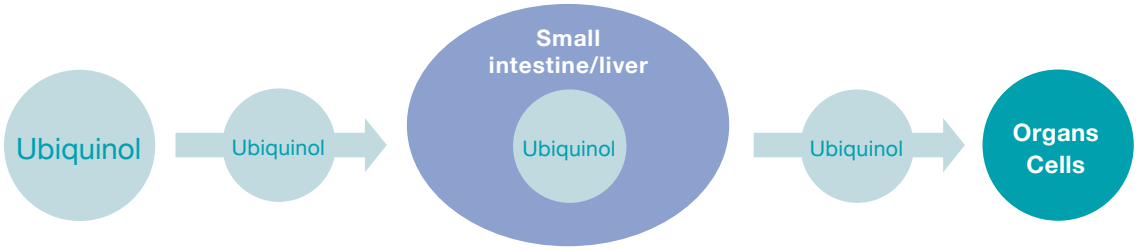
Conventional CoQ10: Oxidized form

CoQ10 **needs to be converted to ubiquinol** in the small intestine/liver by using energy and enzymes before distribution though the bloodstream to the organs such as the heart and kidney.



Ubiquinol: Reduced form

Ubiquinol is directly active as an antioxidant and as an energy production enhancer because ubiquinol does not require the conversion process.



Unfortunately, the production of ubiquinol declines with age, as does the ability to convert ubiquinone to ubiquinol.[52] This impaired production and conversion is believed to contribute to age-related declines in cellular energy production and function, as well as increased oxidative damage.[53] In these instances, supplementing with stabilised active ubiquinol may be helpful in bridging the gap and supporting the body in balancing oxidative stress and protecting cells against free radical damage.

Ubiquinol – benefits beyond energy

In addition to its role in energy production, ubiquinol is unique in that it is the only endogenously synthesised lipid-soluble antioxidant in human cells. Due to its redox property, ubiquinol has a direct free radical scavenging effect and serves as a powerful antioxidant in mitochondria and lipoprotein lipids present in the circulation, as well as in lipid membranes.[54] Ubiquinol efficiently protects membrane phospholipids from peroxidation and also mitochondrial DNA and membrane proteins from free-radical-induced oxidative damage.[55] Ubiquinol participates in the regeneration of other antioxidants, such as vitamins C and E.[52] Research also highlights its role in modulating gene expression, mitochondrial function and signalling, with important implications in the senescence process and cell death.[45]

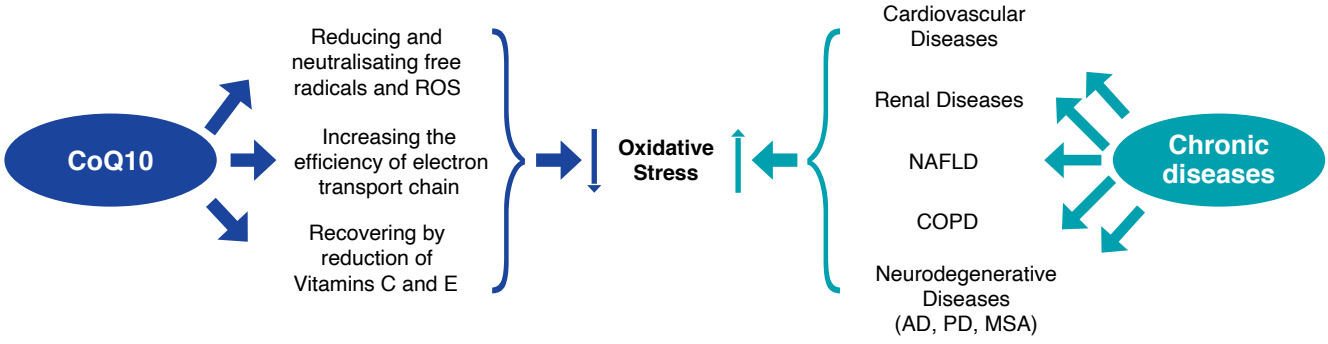
This antioxidant activity appears only with the reduced form of CoQ10, ubiquinol. The oxidised form, ubiquinone, is rapidly reduced to ubiquinol after oral intake.[56]

Ubiquinol's key roles in the body:

- **Plays a central role in mitochondrial oxidative phosphorylation and the production of adenosine triphosphate (ATP).**
- **Functions as an antioxidant in cell membranes and lipoproteins.**
- **Acts as a cell-membrane stabiliser.**
- **Participates in the recycling of other antioxidants such as α-tocopherol and ascorbic acid.**

These roles constitute its broad relevance and potential as an important adjuvant therapy, especially in conditions with mitochondrial dysfunction and oxidative stress, such as some cardiovascular and pulmonary diseases, and in age-related conditions.

Due to its superior bioavailability, ubiquinol is the preferred form of CoQ10 for therapy.[57, 58] It is for this reason that The European Medicine Agency (EMA) has approved ubiquinol for the treatment of primary CoQ10 deficiency.[4]



CoQ10 mechanisms against oxidative stress associate with chronic disease [NALF: non-alcoholic fatty liver disease; COPD: chronic obstructive pulmonary disease; AD: Alzheimer's disease; PD: Parkinson's disease; MSA: multiple system atrophy].[22]

Adapting nutritional medicine to suit patient needs

The COVID-19 pandemic has had a significant impact on many aspects of life across the globe, and its effects are expected to last well into the future. One positive consequence of the pandemic is that consumers now place an even greater value on good health and are taking more steps to proactively manage their physical and mental wellbeing. In their quest for better physical and mental wellbeing, customers are seeking high-quality information from reputable sources. This all presents an opportunity for healthcare professionals to offer authentic, science-backed information to their customers.

Understanding the complexity of the diverse roles of mitochondria is of particular significance for healthcare across all life stages and could provide insight into individual responses to diet, lifestyle, medication, and other environmental exposures.[40] While the scientific community has long been aware of the important role that mitochondria play in health, it is only now that consumers are starting to recognise this fundamental aspect of health and wellbeing.

Ubiquinol – what are the heart-health benefits?

Cardiovascular diseases cause approximately one-third of deaths worldwide.[59] Numerous studies have demonstrated that ubiquinol supplementation significantly improves endothelial function, as measured by flow-dependent endothelial-mediated dilation, which may translate to a 10-25% reduction in residual cardiovascular risk in people both with and without established cardiovascular disease.[60]

Those aged 40-65 years are a rapidly expanding group seeking preventative information to support healthy ageing, particularly in relation to heart health. Unfortunately, the body's natural levels of myocardial ubiquinol decline significantly with age, resulting in increased levels of oxidative stress and a greater susceptibility to cardiovascular disease.[61] This age group are also the main users of statin medications, a commonly prescribed class of drugs known to deplete plasma ubiquinol levels even further.[46, 62]

Ubiquinol supplementation has been shown to be an effective strategy to improve heart health in those over 40 years.

In addition to its action in mitochondrial energy production required for healthy heart muscle function, ubiquinol also works as a potent antioxidant. The antioxidant action is two-fold: firstly, protecting myocardial cells against potential damage from oxidants, and secondly by reducing oxidant production that could potentially cause damage. Furthermore, ubiquinol supplementation promotes improved cardiovascular relaxation by balancing oxidative and reductive reactions, important in protecting the heart muscle from free radical damage.[4,48,62]

The heart is the major consumer of energy in the body on a weight basis.[63] As such, the bioenergetic effects of ubiquinol are of fundamental importance in cells such as cardiac myocytes, due to their high metabolic demand.[64]

Ubiquinol ameliorates endothelial dysfunction in subjects with mild-to-moderate dyslipidaemia

A randomised, double-blind, single-centre trial was conducted to investigate changes in endothelium-dependent vasodilation induced by ubiquinol in healthy subjects with moderate dyslipidaemia.[65] Subjects with no clinical signs of cardiovascular disease, moderate endothelial dysfunction (as measured by flow-mediated dilation (FMD) of the brachial artery), not taking any lipid-lowering treatments and with low-density lipoprotein (LDL) cholesterol levels of between 130–200 mg/dL, were randomised to receive either 100 mg/day or 200 mg/day of ubiquinol or placebo for 8 weeks. At the end of the trial period and compared to the placebo group, those receiving 100 mg and 200 mg ubiquinol supplementation had significantly increased plasma CoQ10 levels ($p<0.001$) and FMD and serum nitrate and nitrite levels ($p<0.001$ and $p=0.016$, respectively), while LDL oxidation lag time improved significantly in those receiving 200 mg/day ubiquinol. These results indicate that ubiquinol supplementation is an effective treatment approach for ameliorating dyslipidaemia-related endothelial dysfunction.

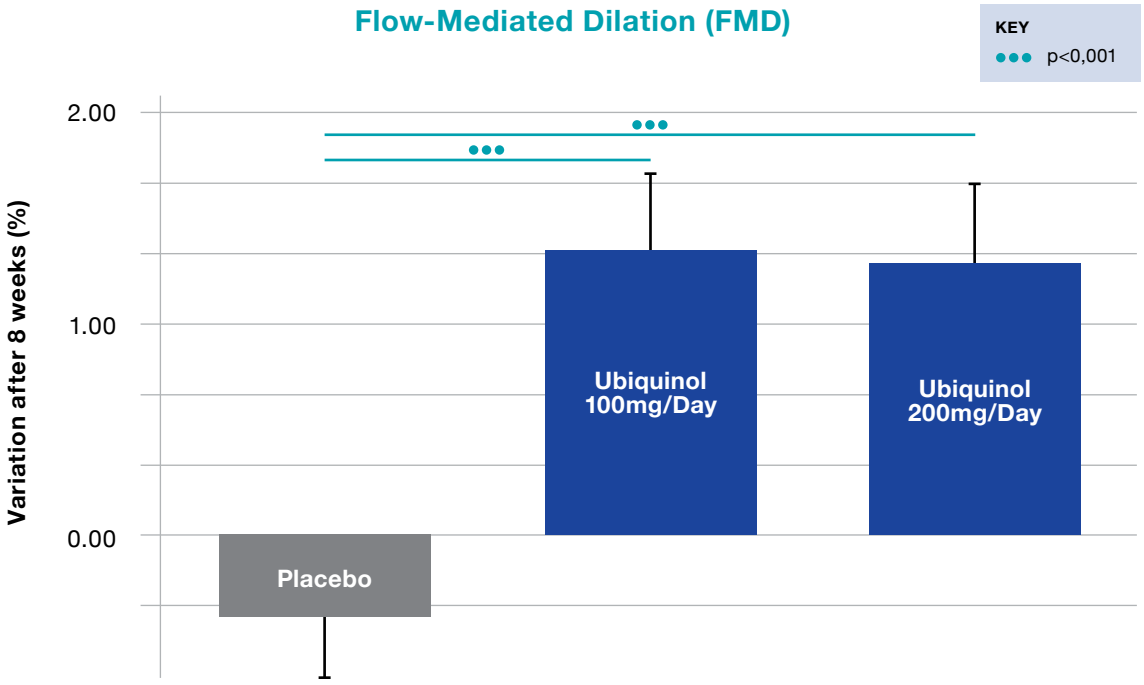
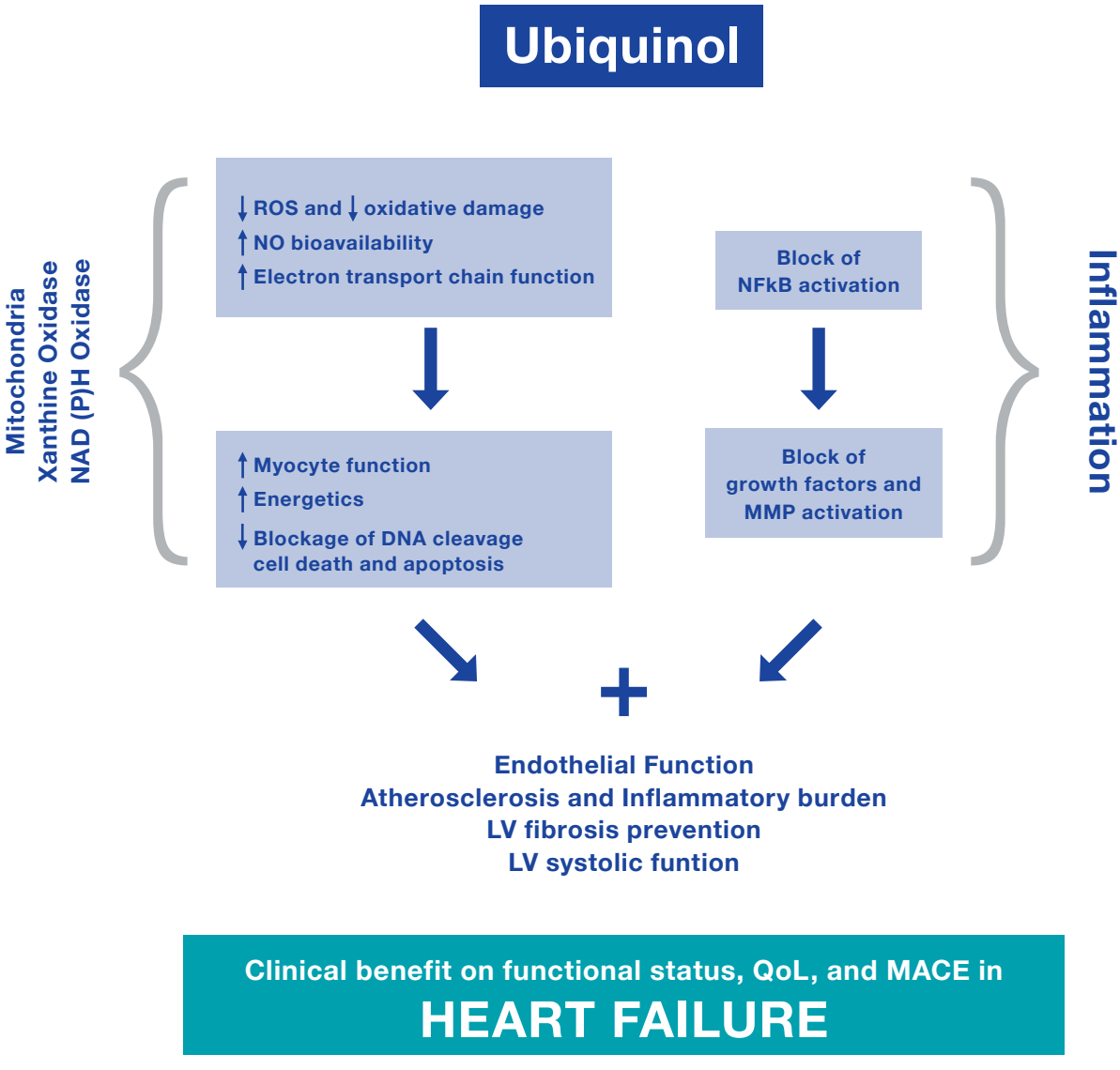


Figure 1. Ubiquinol supplementation improves endothelial function in healthy subjects with cardiovascular risk factors.


OH
H3CO
H3CO
CH3
OH

Heart Failure

Reduced levels of mitochondrial oxidative phosphorylation with reduced energy reserve are contributing factors in the progression of heart failure.[66] Low levels of CoQ10 have been found in up to 75% of patients with diabetic cardiomyopathy, ventricular or atrial septal defects, mitral stenosis or insufficiency, and aortic stenosis or insufficiency.[46] Depletion of myocardial ubiquinol has been observed in heart failure patients, with the severity of this deficiency correlating with symptom severity.[46,64]



Adapted from: Di Lorenzo et al. Clinical Evidence from C10 Coenzyme Supplementation in Heart Failure: From Energetics to Functional Improvement. J. Clin. Med. 2020, 9, 1266.

Ubiquinol improves endothelial function in patients with heart failure with reduced ejection fraction

In a randomised, double-blind, placebo-controlled, crossover pilot study, 14 patients with stable heart failure with reduced ejection fraction were allocated to ubiquinol 400 mg/day or placebo for 3 months.[67] Patients were crossed over to the alternative treatment after a 1-month washout period. Before and after each treatment, peripheral endothelial function was assessed using the reactive hyperemia index (RHI) and analysed using the natural logarithm of RHI (LnRHI). At the end of the 3-month trial period, ubiquinol supplementation resulted in significant and clinically meaningful improvement in peripheral endothelial function in patients with heart failure, as compared to placebo **(Figure 2).**

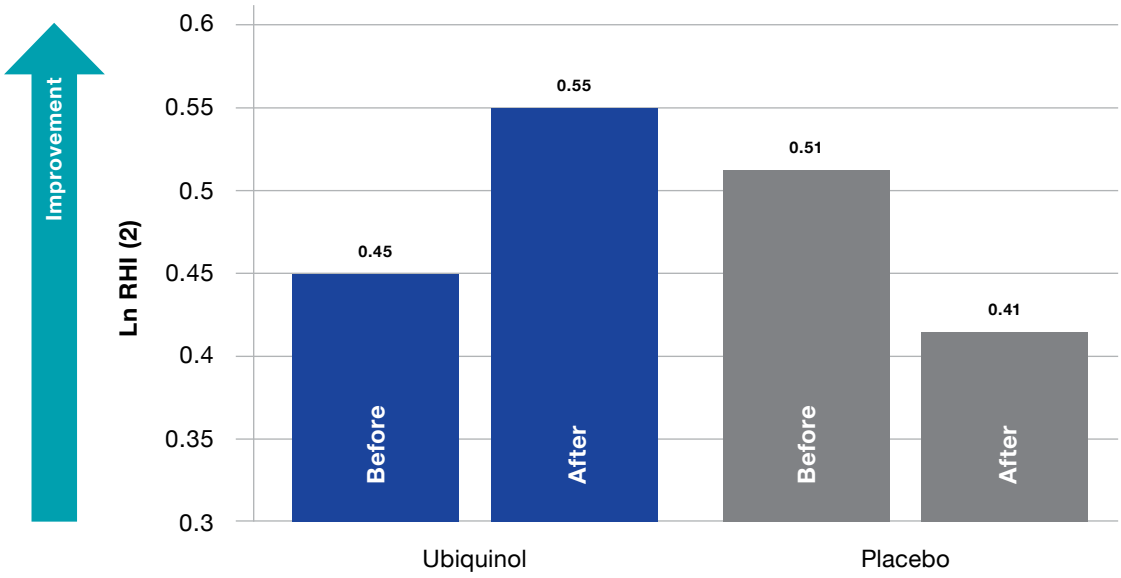


Figure 2. Ubiquinol supplementation improves endothelial function in heart failure patients.

Ubiquinol supplementation improves clinical outcomes in patients with heart failure with preserved ejection fraction (HFpEF)

A phase 2 randomised, double-blind, placebo-controlled trial was carried out in order to determine if supplementing with ubiquinol (600 mg/d) and/or D-ribose (15 g/d) could improve cardiac performance and reduce symptoms in patients (n=216) with HFpEF who were over 50 years of age with a left ventricular ejection fraction (EF) > 50%.[125] The study was conducted over 12 weeks and involved four study groups:

- Group 1 (placebo): placebo ubiquinol capsules and placebo D-ribose powder
- Group 2 (ubiquinol): ubiquinol capsules (600 mg/d) and placebo D-ribose powder
- Group 3 (D-ribose): placebo ubiquinol capsules with D-ribose powder (15 g/d)
- Group 4 (ubiquinol + D-ribose): ubiquinol capsules (600 mg/d) and D-ribose powder (15 g/d)

The seven outcome measures for this study included (1) The Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score, (2) level of vigor using a subscale from the Profile of Mood States, (3) EF, (4) the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (septal E/e' ratio), (5) B-type natriuretic peptides, (6) lactate/adenosine triphosphate ratio, and (7) the 6-minute walk test.

At the end of the trial period, treatment with ubiquinol and/or D-ribose significantly improved the KCCQ clinical summary score (17.30 to 25.82 points), vigor score (7.65 to 8.15 points), and EF (7.08% to 8.03%) and reduced B-type natriuretic peptides (-72.02 to -47.51) and lactate/adenosine triphosphate ratio (-4.32 to -3.35x 10^{-4}). There were no significant increases in the septal E/e' or the 6-minute walk test. These findings support the use of these ubiquinol and D-ribose in addition to standard therapeutic treatments for reducing symptoms and increasing EF in patients with HFpEF.

Ubiquinol and statins – what you need to know

Statins are the most commonly used class of lipid-modifying agents worldwide, and for decades have been the primary prevention treatment for cardiovascular disease in patients with significant hypercholesterolaemia or high CVD risk.[68] Statins work by impairing skeletal muscle and myocardial bioenergetics via the inhibition of the key enzyme in the mevalonate pathway, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, necessary for the production of both cholesterol and ubiquinol.[46, 62]

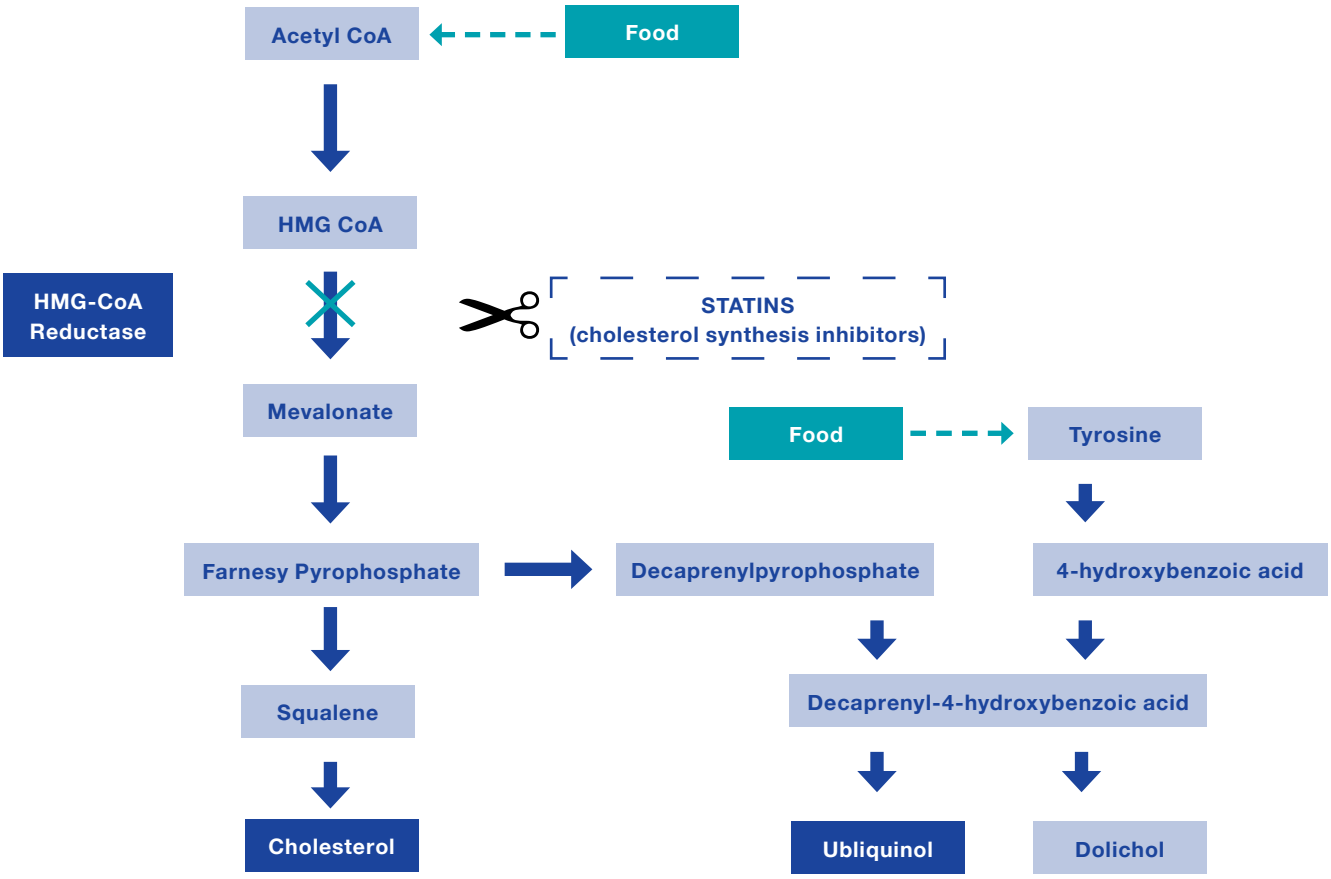


Figure 3. Inhibition of ubiquinol synthesis by statin therapy. (Bentinger M et al., BBRC 396: 74-79, 2010)

Statin therapy and plasma ubiquinol concentrations

A recent meta-analysis evaluated the impact of statin therapy on plasma CoQ10 concentrations,[69] **with around 95% of plasma CoQ10 known to be in the form of ubiquinol.[9]** The data from 8 placebo-controlled treatment arms suggested a significant reduction in plasma ubiquinol concentrations following treatment with statins, independent of statin formulations, duration, or dose **(Figure 4)**.

Study name	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Paiva et al., 2005a	-0.550	0.105	0.011	-0.756	-0.344	-5.235	0.000
Paiva et al., 2005b	-0.530	0.093	0.009	-0.713	-0.347	-5.680	0.000
Ashton et al., 2011	-0.490	0.090	0.008	-0.667	-0.313	-5.423	0.000
Oranje et al., 2001	-0.270	0.103	0.011	-0.472	-0.068	-2.615	0.009
Jula et al., 2002	-0.320	0.424	0.180	-1.152	-0.512	-0.754	0.451
Strey et al., 2005	-0.390	0.151	0.023	-0.685	-0.095	-2.591	0.010
Ghirlanda et al., 1993a	-0.430	0.135	0.018	-0.695	-0.165	-3.185	0.001
Ghirlanda et al., 1993b	-0.400	0.100	0.010	-0.595	-0.205	-4.015	0.000
	-0.455	0.040	0.002	-0.523	-0.376	-11.139	0.000

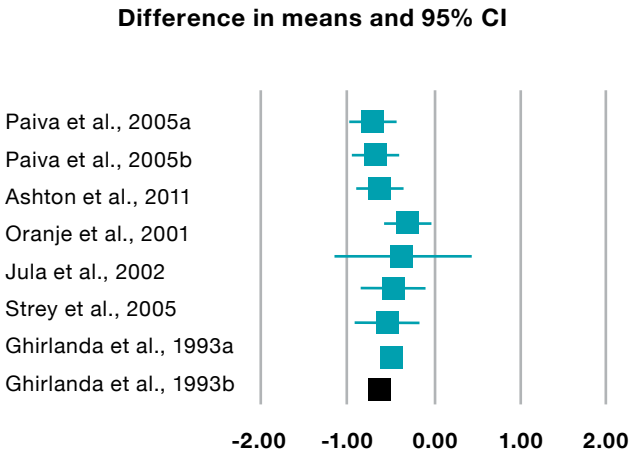


Figure 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma ubiquinol concentrations. Lower plot shows leave-one-out sensitivity analysis.

Similar results were observed in a study evaluating to what extent plasma CoQ10 levels change following atorvastatin therapy.[70] Individuals without dyslipidaemia or known cardiovascular disease received atorvastatin 80 mg daily for 16 weeks. Blood samples collected at baseline and after 4, 8, and 16 weeks of treatment were assayed for CoQ10. At the end of the trial period, plasma CoQ10 decreased 45% (p<0.001) **(Figure 5).**

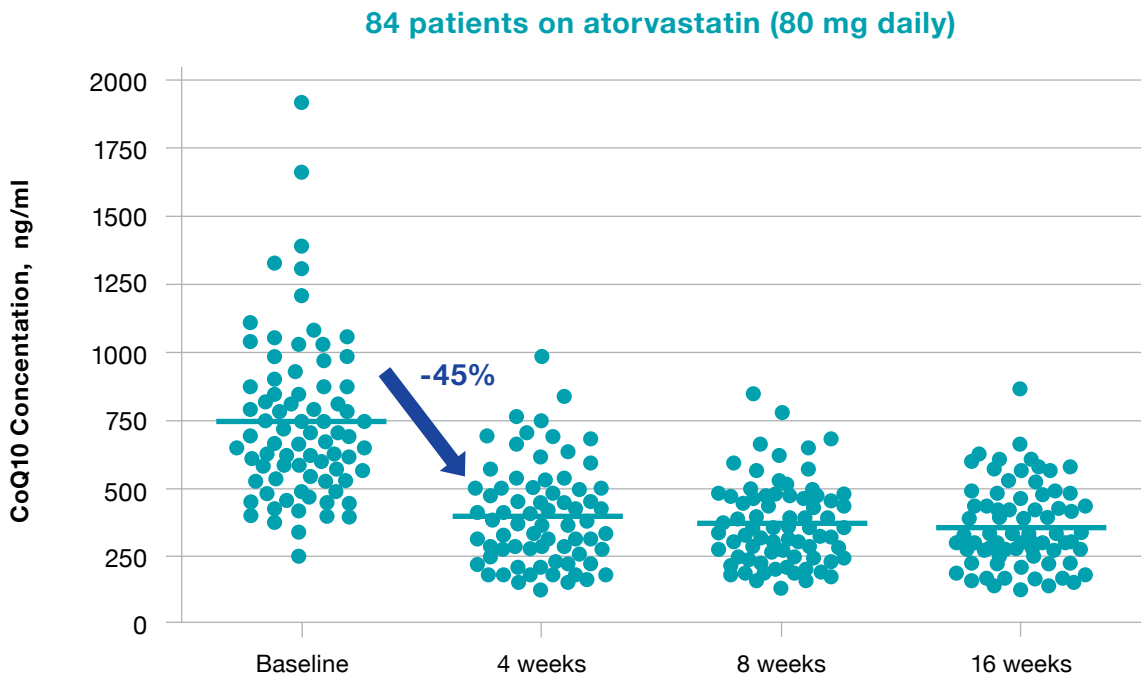


Figure 5. Changes in plasma CoQ10 concentrations after 4, 8, and 16 weeks of atorvastatin. Each dot represents an individual study participant, and the lines represent the mean values.

The role of ubiquinol in statin-associated myopathy

Multiple studies have demonstrated that statin medications reduce plasma levels of CoQ10,[70, 71] and that side effects of fatigue and myalgia, commonly seen in statin therapy, may be a result of ubiquinol depletion.[71-74] Studies have also demonstrated that oral supplementation of CoQ10 alongside statin medications can still effectively raise serum levels[75] and will work to negate some of the harmful drug effects.[46,76] For example, in a study conducted to demonstrate the effect of CoQ10 supplementation in patients with statin myopathy, it was found that after 6 months of CoQ10 coadministration plasma CoQ10 levels increased by more than 194% ($p<0.001$), pain decreased on average by 53.8% ($p<0.0001$), and muscle weakness decreased by 44.4% ($p<0.001$) **(Figure 6)**.[77] As such, ubiquinol supplementation is an important adjunct therapy to be considered for patients on statins, particularly for those with chronic heart failure and decreased myocardial function.[64]

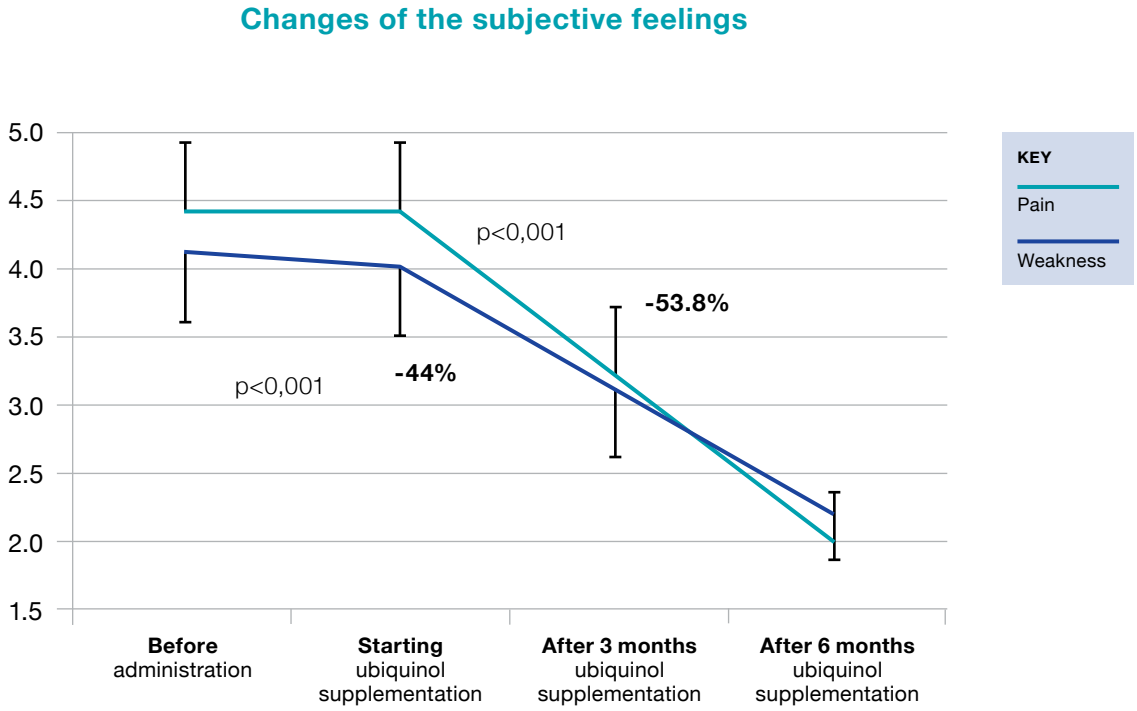


Figure 6. Reductions in pain and weakness following 6 months of supplementation with CoQ10 in patients with statin myopathy.

Pulmonary co-morbidity considerations

It is well known that acute pulmonary infections have the potential to destabilise cardiac diseases such as heart failure.[78] Although the role of ubiquinol supplementation for patients with pulmonary diseases is yet to be established as standard care, there is clear involvement of ROS in the pathophysiology of lung disease.[28]

Research has shown that ubiquinol supplementation at a daily dose of 300 mg, provided improved right and left ventricular heart function in patients with Pulmonary Arterial Hypertension, and an improvement in haemoglobin production and red cell maturation.[79] Such results highlight the beneficial role of ubiquinol supplementation in individuals with depressed myocardial function and underlying mitochondrial dysfunction.

Table 2. Mechanism of action of ubiquinol in various cardiovascular diseases:[46]

ACTION OF UBIQUINOL
Improvement in cardiac bioenergetics
Free radical scavenger and antioxidant action
Improvement in endothelial function and vasodilation
The precursor of CoA
Reduction in pro-inflammatory cytokines
Membrane stabilisation action
Preservation of myocardial Na+/K+ ATPase pump
Anti-viscosity effect

3

FUELLING FERTILITY

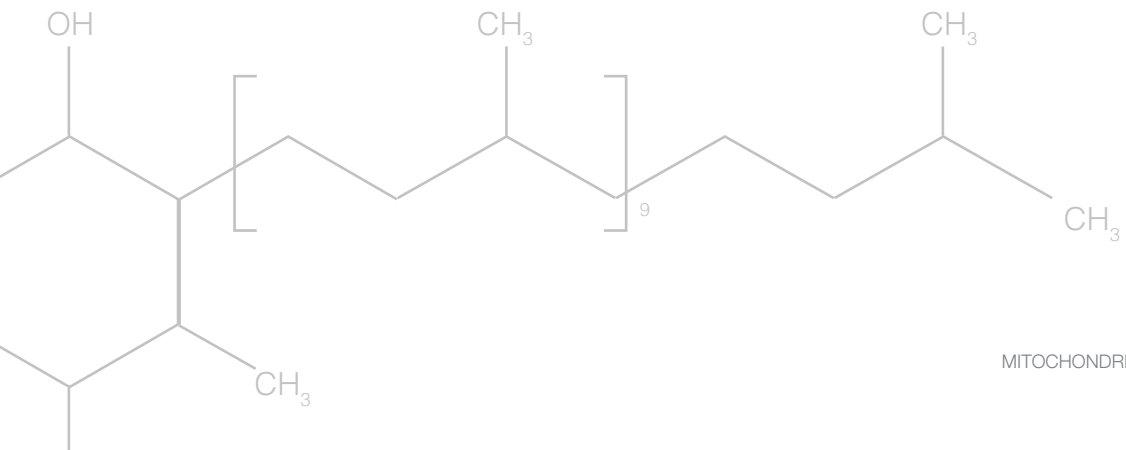
Infertility currently affects one out of six couples worldwide and represents one of the great challenges of modern healthcare.[80,81] Ageing decreases fertility for both males and females, with male fertility declining less rapidly. However, male factors, either fully or in part, are attributed to half of all infertility issues.[82] One of the key contributing factors to infertility is reduced sperm counts. For example, according to a 2017 meta-analysis, sperm counts among men in North America, Europe, Australia and New Zealand declined by more than 59% from 1973 to 2011.[83] Diminishing ovarian reserves and oocyte quality play a significant role in the pathophysiology of female infertility.[80]

Young adults are becoming more conscious of maintaining their health both now and into the future, with an increasing number proactively seeking credible information from reputable sources regarding their health. Unfortunately, the challenge of balancing the demands of life can often derail even the best of intentions, leading to irregular eating patterns, chronic stress, sleeping disorders and increased fatigue – all of which can negatively impact egg and sperm health.

Due to its potent antioxidant effects, supplementing with ubiquinol has been demonstrated to play a beneficial role in supporting fertility and improving pregnancy outcomes, and should be a key recommendation for couples planning a family.

The role of oxidative stress on fertility

Oxidative stress and mitochondrial dysfunction are among the most investigated mechanisms for reduced fertility.[82, 84] Low ubiquinol levels have been associated with several conditions determining infertility.[82] Improving mitochondrial function by supplementing antioxidants such as ubiquinol has been proposed as one of the important strategies to enhance reproductive performance.[82, 84]



Male fertility

One of the key requirements for sperm motility and velocity is the amount of energy available, thus, sperm require exceptionally high amounts of ATP, for which ubiquinol is critical.[85] Because of this increased need for energy, it has been shown that an increase in sperm motility requires a parallel increase in mitochondrial activity.[85] Mitochondrial dysfunction can impact the sperm cell's ability to produce ATP energy and significantly decreases sperm motility.[7] Moreover, high mitochondrial activity levels have been shown to increase the success in vitro fertilization rate.[86] These studies suggest that human sperm motility correlates with mitochondrial functional status.[85]

A growing body of evidence has highlighted the role of oxidative stress in disorders of spermatogenesis, with 30–80% of infertile men having elevated seminal reactive oxygen species levels (ROS).[82] While moderate concentrations of ROS are necessary to ensure normal cellular functions such as sperm capacitation, hyperactivation, acrosome reaction and sperm-oocyte-fusion, when ROS levels exceed the antioxidant capacity of seminal fluid, oxidative stress occurs and causes DNA fragmentation and sperm apoptosis.[82] Spermatozoa are particularly susceptible to oxidative stress because their plasma membrane is rich in polyunsaturated fatty acids that undergo lipid peroxidation, which in turn increases ROS production. The potent antioxidant properties of ubiquinol work to improve the antioxidant capacity of seminal fluid and counteract elevated levels of oxidative stress by reducing ROS production in mitochondria, thus protecting spermatozoa membranes from lipid peroxidation.[82]

The protective role of ubiquinol on sperm health parameters

Multiple studies on the effects of ubiquinol on sperm health parameters have shown a positive influence on sperm concentration, morphology, and motility **(Figure 7)**.[87-89]

	Safarinejad MR[87] RCT	Thakur AS[89] Open study	Alahmar A[88] Open study	
Number of subjects	114/group	60	35	30
Ubiquinol supplementation	200 mg/day 26 weeks	150 mg/day 6 weeks	200 mg/day 3 months	400 mg/day 3 months
Sperm concentration[#)]	81.6 % ↑↑↑	51.2 % ↑↑	52.4 % ↑↑	62.7 % ↑↑
Total motility	31.7 % ↑	26.0 % ↑	16.7 % ↑	48.4 % ↑↑
Progressive/rapid motility[#)]	Not available	40.7 % ↑↑	36.5 % ↑↑	83.5 % ↑↑↑
Normal Morphology[#)]	24.0 %[##] ↑	Not available	6.6 % ↑	11.2 % ↑

[#)] increase from baseline [##)] Compared with placebo

Figure 7. Ubiquinol effect on sperm parameters.

A study assaying ubiquinol content in seminal plasma and seminal fluid from 32 subjects with a history of infertility showed a significant correlation between ubiquinol content and sperm count, demonstrating that ubiquinol is needed in seminal plasma in order to counteract peroxidation processes and prevent oxidative damage of sperm cells **(Figure 8).**[90]

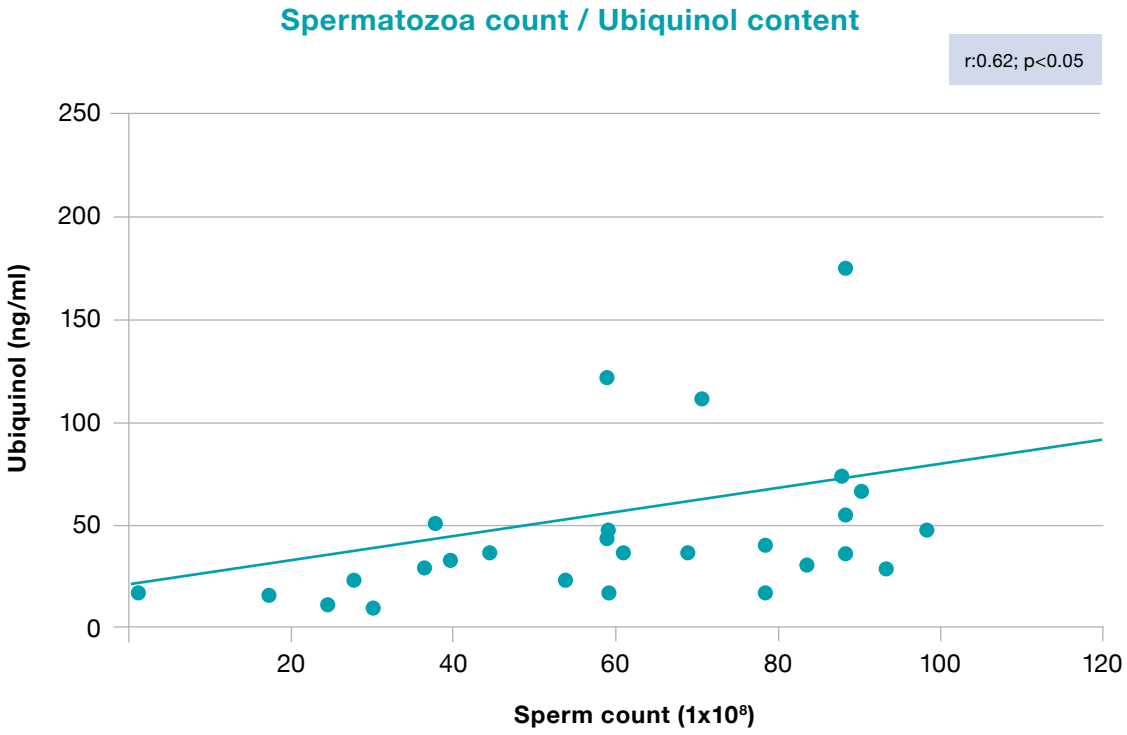


Figure 8. Ubiquinol effect on sperm count.
(R. Alleva et al. Molecular Aspects of Medicine, Vol 18 Sup 1, 1997, p221-228)

Summary of ubiquinol and male fertility [81, 87]

- Ubiquinol is important in maintaining the health, motility and production of sperm.
- Supplementation of ubiquinol has been shown to improve sperm density and motility whilst protecting DNA and improving male fertility.
- Sperm cell mitochondria have high concentrations of ubiquinol, playing an integral role for the production of ATP.
- Healthy sperm count and motility have been correlated with healthy ubiquinol levels.

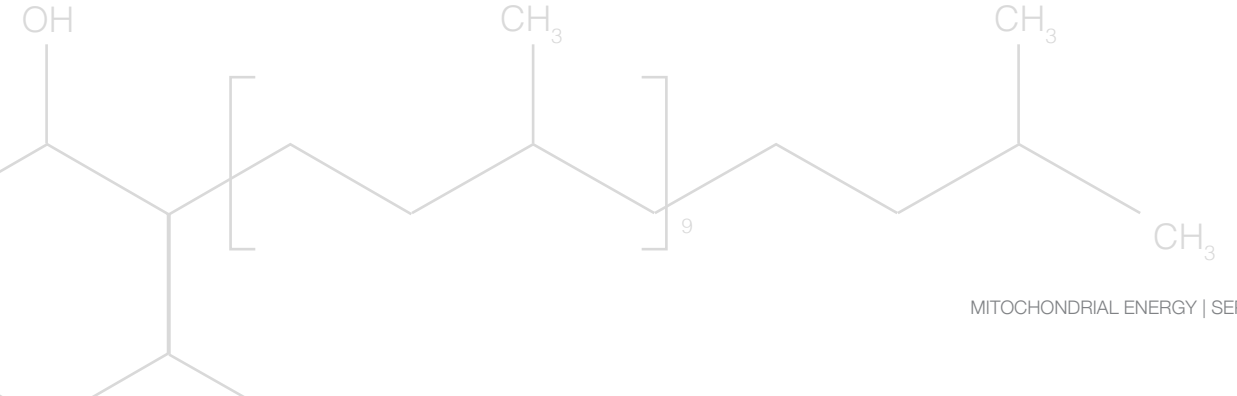
Female fertility

Mitochondria are the most abundant organelles in oocytes and early embryos, and research indicates that mitochondrial energy may influence female fertility.[84] Mitochondrial function and dysfunction have been the subject of various studies in ovarian ageing and metabolic stress due to the fundamental role that mitochondria play in egg maturation, cell division in the embryonic stage, and embryo development and implantation in the uterus – processes that all require abundant energy supply.[91] Suboptimal ubiquinol availability has been proposed as one factor that can drive age-associated oocyte deficits causing infertility.[92]

Increased oxidative stress has also been identified as being responsible for the initiation or development of pathological processes that negatively impact female fertility.[80] Reactive oxygen species affect the many functions of the ovary, including oocyte maturation, ovulation, and implantation.[93] Oxidative stress may also be linked to several disease states affecting female fertility, including endometriosis and polycystic ovarian syndrome (PCOS).[94]

CoQ10 supplementation improves fertility outcomes in women undergoing assisted reproductive technology procedures

Due to its powerful antioxidant capacities, ubiquinol plays a critical role in protecting oocytes from oxidative stress and it's for this reason that CoQ10 supplementation has long been used to ameliorate infertility outcomes.[80] According to a recent systemic review and meta-analysis of clinical studies regarding the effect of CoQ10 in women with infertility undergoing assisted reproductive technologies (ART), oral supplementation of CoQ10 increased clinical pregnancy when compared with placebo or no treatment (28.8% vs. 14.1% respectively), without an effect on live birth or miscarriage rates **(Figure 9)**.[80] Supplementation of CoQ10 has also been demonstrated to improve ovarian response to stimulation and embryological parameters in young women with poor ovarian reserve in IVF-ICSI cycles.[84]



	CoQ10		Control		Odds Ratio		
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95%CI**	**Year**
El Refaeey 2014	19	51	3	50	17.3%	9.30 [2.54, 34.06]	2014
Bentov 2014	6	17	6	22	16.0%	1.45 [0.37, 5.71]	2014
Caballero 2016	6	39	5	39	17.6%	1.24 [0.34, 4.45]	2016
Xu 2018	24	76	16	93	34.6%	2.22 [1.08, 4.58]	2018
Sen Sharma 2019	7	32	3	30	14.5%	2.25 [0.59, 10.83]	2019
Total (95% CI)		**215**		**234**	**100.0%**	**2.44 [1.30, 4.59]**	
Total events	62		33				
Heterogeneity: $Tau^2 = 0.16$, $Chi^2 = 5.85$, df = ($P = 0.21$); $I^2 = 32\%$							
Test for overall effect: $Z = 2.77$ ($P = 0.006$)							

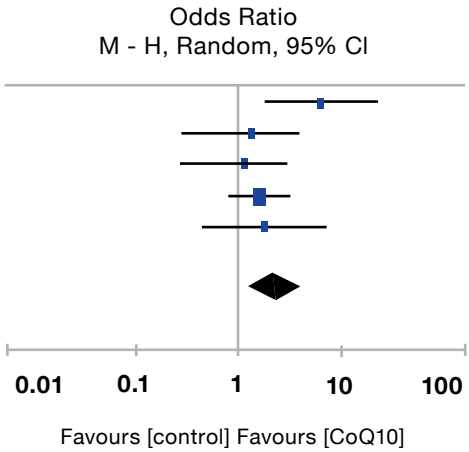


Figure 9. Forest plot of the effect of CoQ10 supplementation on clinical pregnancy rate in women with infertility undergoing assisted reproductive technology in comparison with placebo or no-treatment (control)

Effect of ubiquinol on serum reproductive hormones of amenorrheic patients

Functional Hypothalamic Amenorrhea (FHA) is a major cause of female infertility. It is the absence of a menstrual period in a woman of reproductive age due to a disruption in the hormones produced by the hypothalamus in the brain. This impairment in the hypothalamic-pituitary–ovarian axis leads to anovulation and hypoestrogenism. Oxidative stress is one known factor related to FHA.

Due to ubiquinols' powerful antioxidant effects, a study was conducted to determine the role of ubiquinol on reproductive hormones FSH and LH in amenorrheic patients.[95] A group of 50 FHA infertile female patients between the ages of 20 – 40 years were given 150mg of ubiquinol daily for 4 months. At the end of the trial period, FSH concentration had increased three-fold ($p<0.05$) and LH concentration doubled ($p<0.05$) **(Figure 10 and 11)**. The results found that the antioxidative properties of ubiquinol may work to improve the secretion of FSH and LH Levels among infertile females.[95]

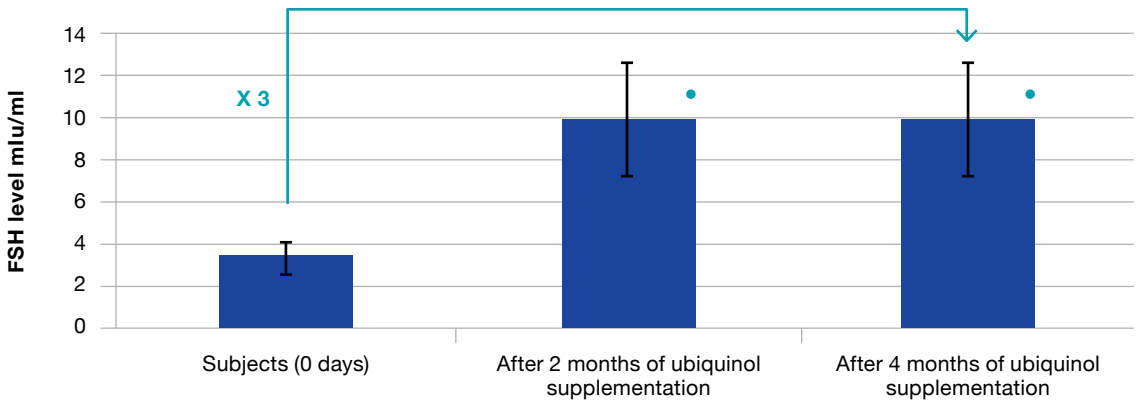


Figure 10. Ubiquinol supplementation increases FSH levels three-fold ($p<0.05$).

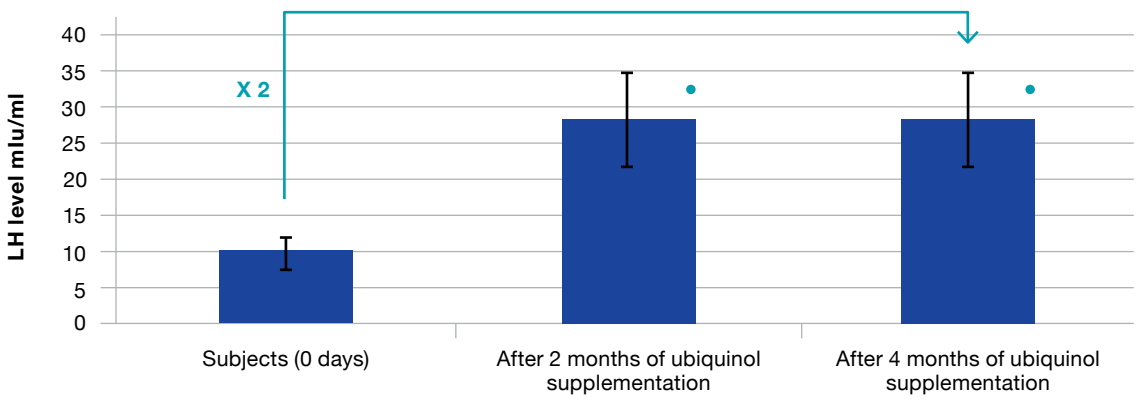


Figure 11. Ubiquinol supplementation increases LH levels two-fold ($p<0.05$).

4

ENERGY, ENDURANCE AND RECOVERY

Athletes and fitness enthusiasts, who place a premium value on maintaining their health and wellbeing, are seeking solutions that will help give them a competitive edge. Due to its important role in energy metabolism and as an antioxidant, ubiquinol has received much attention in sports nutrition as a means to reduce oxidative stress and muscle damage and to enhance performance.[96]

While regular physical activity is beneficial and associated with a lower risk of all-cause mortality,[97] prolonged and intensive exercise is known to generate oxidative stress-inducing conditions in the body and to contribute to muscle damage.[98,99]

Fatigue occurs when cells and tissues are damaged by reactive oxygen species generated during excessive activity, combined with an accumulation of cellular waste products. Recovery from fatigue can only happen when this cellular damage is adequately repaired.[100] Accordingly, providing targeted antioxidant supplementation that works to inhibit damage from oxidative stress and which can stimulate mitochondrial energy production, is an effective strategy against fatigue.[100]

A direct link between physical performance and blood and muscle tissue ubiquinol levels

The data available in the scientific literature have provided a direct link between physical performance and blood and muscle tissue ubiquinol levels.[101] Fatigue and exercise endurance has been shown to be improved in healthy subjects supplemented with ubiquinol.[102,103] In one study, oral supplementation of ubiquinol during high-intensity exercise was found to reduce the overexpression of pro-inflammatory cytokines and increase anti-inflammatory cytokines, indicating a possible role in modulating exercise-induced inflammation.[101]

Short-term ubiquinol supplementation reduces oxidative stress associated with strenuous exercise in healthy adults

In a second study, short-term (2-week) oral supplementation with ubiquinol was assessed for its ability to diminish muscle dysfunction and free radical generation associated with high-intensity exercise.[104] The participants (healthy and well trained, but not on an elite level) were classified into two groups: ubiquinol and placebo group. The results demonstrated that supplementation with ubiquinol before strenuous exercise decreased oxidative stress and increased plasma nitric oxide, which is known to improve endothelial function, energetic substrate supply, and muscle recovery after strenuous exercise.


CH3
CH3
CH3

Ubiquinol supplementation enhances peak power production in trained athletes

A double-blind, placebo-controlled study was conducted on 100 well-trained athletes to investigate the effect of ubiquinol supplementation on physical performance, as measured by maximum power output. The participants received either 300 mg ubiquinol or a placebo for six weeks.[105] While both the placebo and ubiquinol groups significantly increased their physical performance over the treatment period as a result of the training regime itself, ubiquinol supplementation significantly enhanced peak power production in comparison to placebo **(Figure 12).**

Effects of ubiquinol supplementation on exercise performance

Long-term CoQ10 supplementation has been shown to increase both plasma CoQ10 concentrations and the time to exhaustion.[106] Such outcomes are proposed to be due to a combination of enhanced oxidative phosphorylation within the mitochondria and enhanced antioxidant protection, providing further evidence that ubiquinol might have an anti-fatigue effect and could improve physical exercise capacity.

A separate German study of elite athletes found that daily supplementation of ubiquinol for six weeks had a significant effect in enhancing their physical performance and peak power output as compared to placebo.[107] As higher CoQ10 plasma levels can be achieved with lower dosages of ubiquinol than with ubiquinone,[108,109] ubiquinol may offer a more convenient treatment approach for athletes wanting to maximise performance.

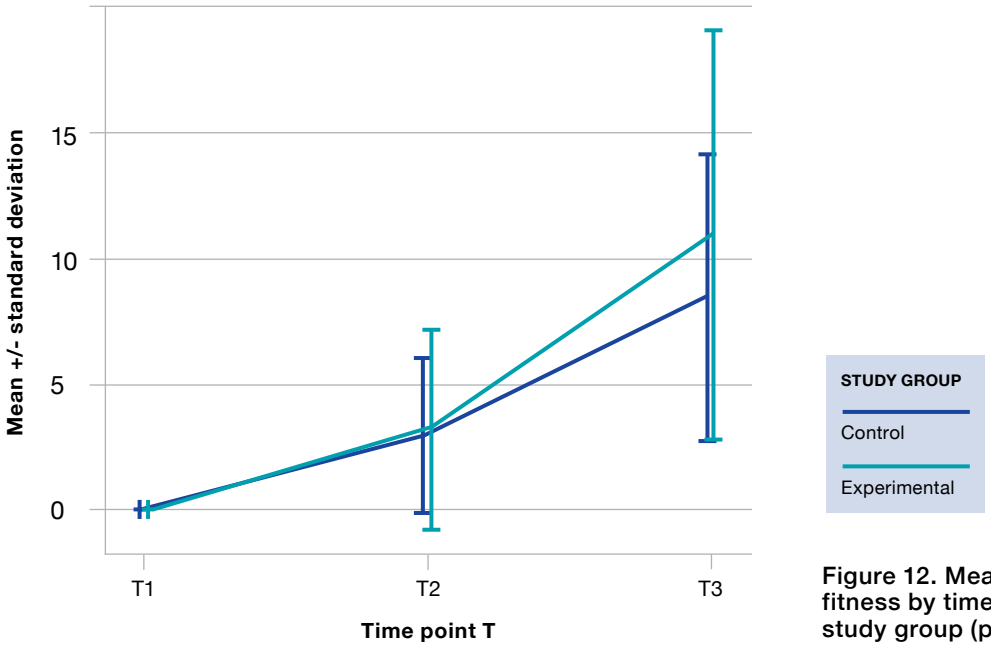


Figure 12. Means of physical fitness by time point and study group (percentage).

Why supporting mitochondrial energy is fundamental for a good night's sleep

Exposure to chronic stress is often associated with sleeping disorders and fatigue syndromes, which eventually lead to more serious disease states.[17]

In our increasingly fast-paced world, no longer are we dedicated to getting a restful eight hours of sleep per night and yet, it is well established, that good sleep is fundamental for health.[110] This increasingly inadequate sleep comes at a cost, with researchers finding that chronically deficient sleep is associated with many negative health outcomes, including poorer mental and physical health, reduced immune function, and an increased risk of cardiovascular problems due to increases in blood pressure and inflammatory markers.[110, 111]

Ubiquinol supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome

In a randomised, double-blinded, placebo-controlled study, researchers found that 150 mg ubiquinol supplementation for 12 weeks improved sleep quality in patients with chronic fatigue syndrome, as well as depression symptoms and arithmetic task performance following a two-month trial period **(Figure 13)**.[112]

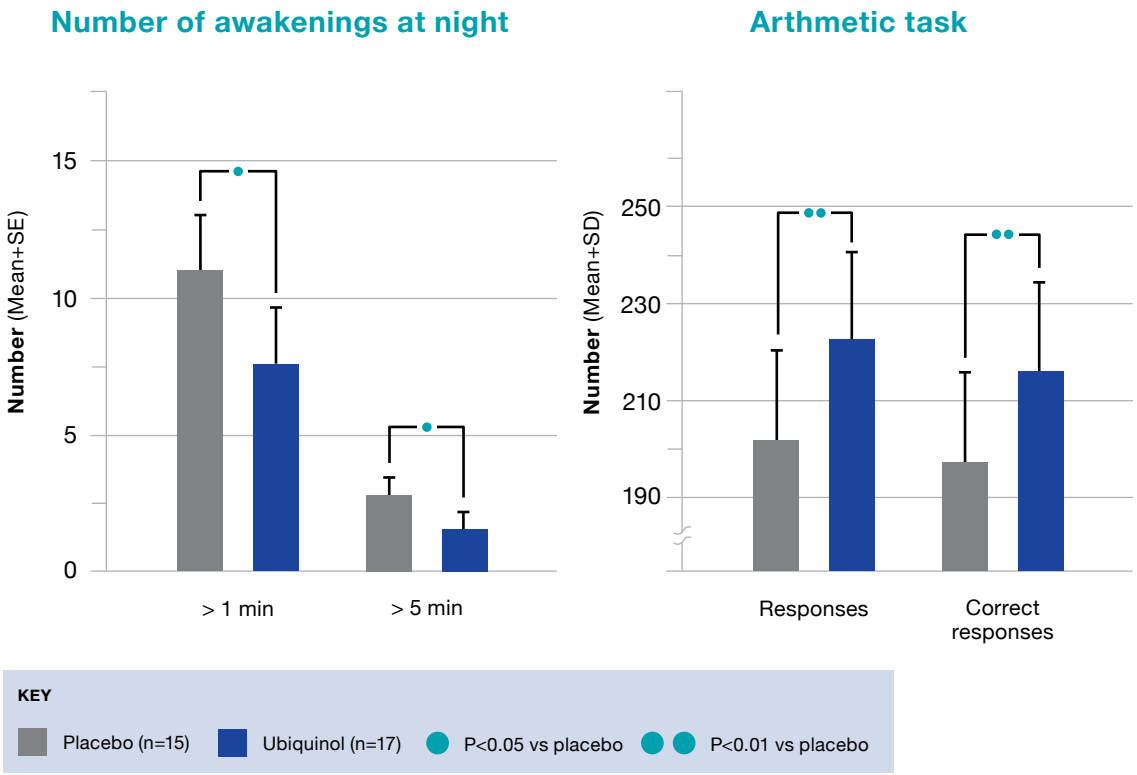


Figure 13. Ubiquinol improves sleep quality and cognitive function in chronic fatigue syndrome.

Ubiquinol relieves daily life stress and improves sleep quality in healthy subjects with high-stress sensitivity

Furthermore, in a randomised, double-blind, placebo-controlled study, researchers examined the effects of ubiquinol supplementation at 100mg/day for eight weeks on stress and sleep in healthy people. The results found that ubiquinol reduced stress and helped to initiate and maintain sleep, improved sleep quality and reduced feelings of fatigue in healthy subjects with relatively high-stress levels **(Figures 14)**.[17] Supplementing with ubiquinol may therefore play a beneficial role in those individuals lacking in energy or who possess high stress but still struggle to find quality sleep.

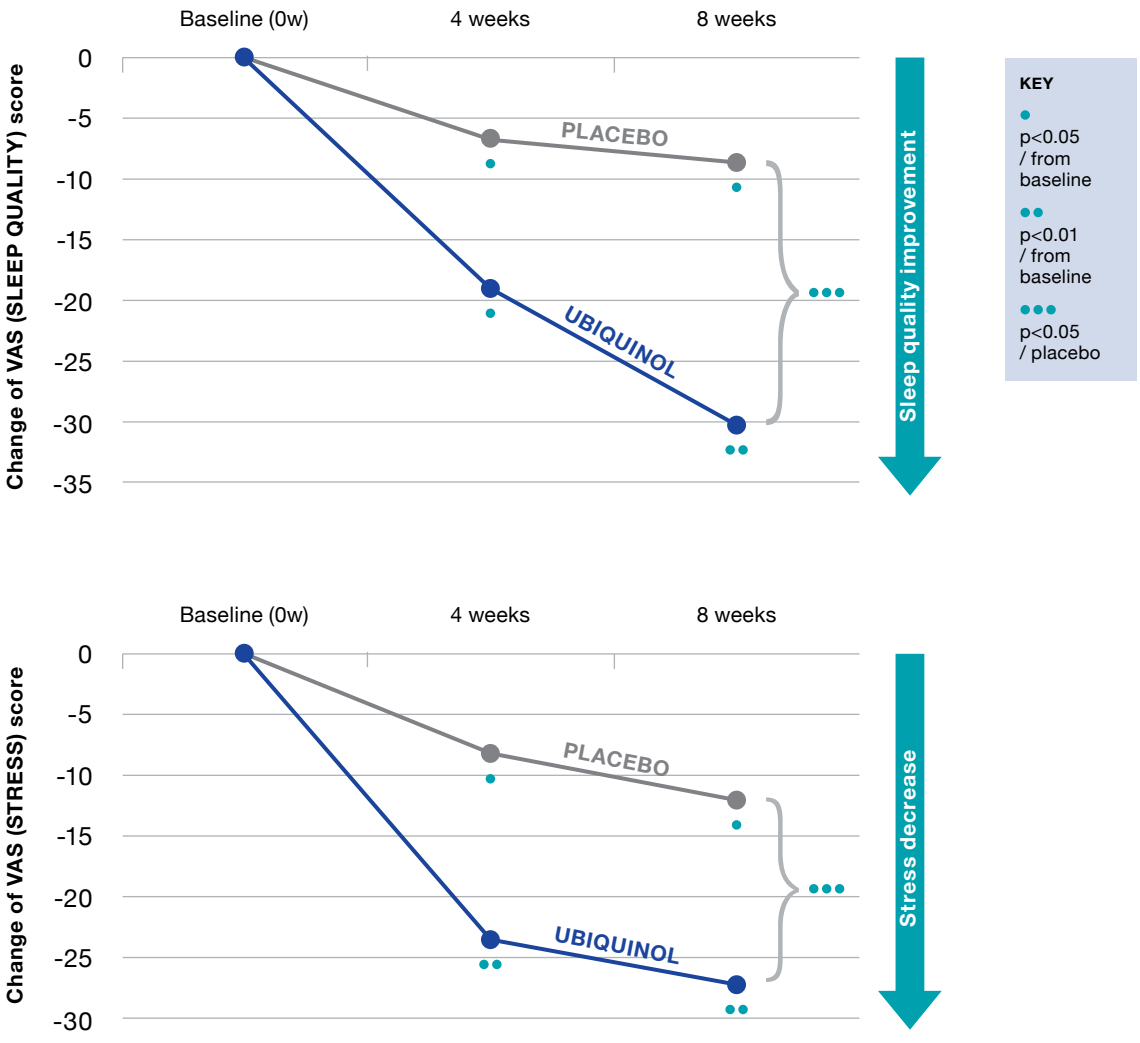


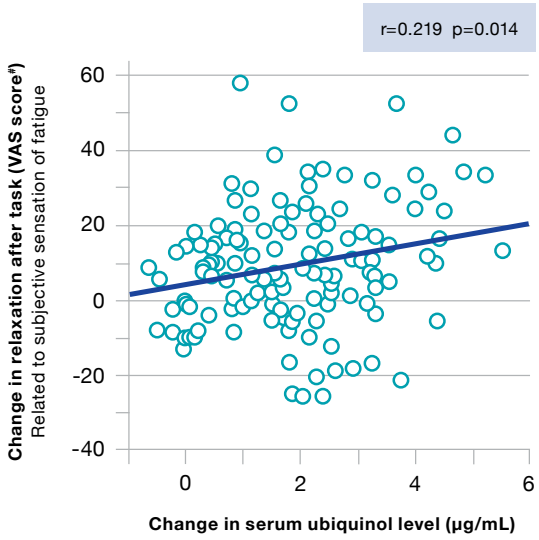
Figure 14. A 100 mg daily supplementation of ubiquinol for 8 weeks reduces daily life stress and improves the quality of sleep in healthy subjects with relatively high stress.

Ubiquinol intake is effective in relieving mild fatigue in healthy individuals

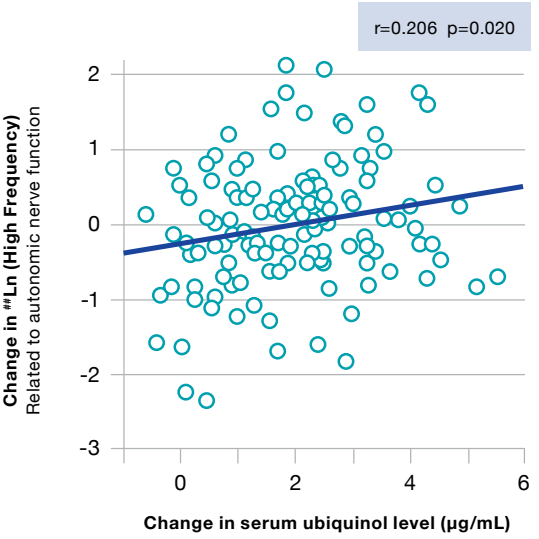
A double-blind, placebo-controlled study evaluated the effects of 100 mg or 150 mg ubiquinol supplementation in healthy individuals experiencing fatigue in daily life that had continued for more than 1 and less than 6 months.[100] At the end of the 12-week trial period, serum ubiquinol levels increased significantly compared to placebo. In both the 100 mg and 150 mg groups, subjective levels of fatigue sensation and sleepiness after cognitive tasks improved significantly compared with those in the placebo group, suggesting an anti-fatigue effect. The 150 mg ubiquinol group also demonstrated significant improvement compared with the placebo group regarding the subjective level of relaxation after task, sleepiness before and after task, motivation for task, and serum level of oxidative stress **(Figure 15).**

Chronic stress has been implicated in mitochondrial dysfunction, which may result in the manifestation of disorders such as cardiovascular diseases, metabolic diseases, neurodegenerative disorders, cancer, aging, and fatigue. As oxidative stress correlates highly with both psychological and physical stress, individuals with higher stress may be more responsive to, and gain greater benefit from, ubiquinol supplementation.[17,18]

Positive corrrelation between the serum ubiquinol increase and the relaxtion after-task improvement



Positive corrrelation between the serum ubiquinol increase and the parasympathetic nerve actvity's growth



VAS is Visual Analogue Scale. It is a questionnaire on subjective symptoms ## (Ln) is Log transformed

Figure 15. Ubiquinol supplementation improves relaxation, cognitive function and autonomic nerve function.

5

WHAT THE PANDEMIC HAS TAUGHT US

The link between immune health and mitochondrial function is now well recognized.[19,113] Mitochondrial dysfunction is strongly correlated to immune dysfunction as all components of the immune system are ATP-dependent.[19,114]

Mitochondrial energy production is a critical component in the synthesis of the macromolecules essential for immune cell function and proliferation, and an adequate supply of ubiquinol is therefore required to enable the various cell types of the immune system to function optimally.[115] Mitochondria also play a fundamental role in regulating signalling pathways and cell fate in both innate and adaptive immune cells.[113] Therapies targeting mitochondrial energy and associated metabolic pathways - instead of exclusively immune-related pathways, have been proposed as one possible approach to repair cellular function and restore immune homeostasis.[113]

Many viruses affect mitochondrial metabolism via alterations in mitochondrial bioenergetics, dynamics, and function. Such damage to the mitochondria results in an increase in the generation of reactive oxygen species, leading to increased oxidative stress and inflammation which, if it becomes excessive, can result in a cytokine storm with widespread tissue damage and potential death.[116] As mitochondria are pivotal in the immune response, it is possible that altered mitochondrial function may explain at least some of the variance in responses to viruses such as influenza and SARS-CoV-2.19 Several clinical studies have linked depleted ubiquinol levels to an increased susceptibility to infection, and intake of CoQ10 has been associated with a significantly reduced risk of hospitalisation from SARS-CoV-2.[115]

Ubiquinol in acute influenza

The World Health Organization estimates up to 5 million cases of severe influenza illness worldwide and attributes between 250,000-500,000 deaths to seasonal influenza outbreaks each year.[117] Due to ubiquinols fundamental role in mitochondrial bioenergetics and immune health, a study was conducted to determine if acute influenza infection was associated with reduced ubiquinol levels compared to healthy controls, and whether there were any associations between ubiquinol levels and illness severity and inflammatory biomarkers.[118]

In a randomised trial spanning three influenza seasons, serum CoQ10 levels were measured in individuals suffering acute influenza as well as in healthy controls.[118] Overall, those with acute influenza had significantly lower serum levels of CoQ10 (p=0.004) **(Figure 16)**. Significantly more patients in the influenza group had low CoQ10 levels (< 0.5 µg/mL) compared to controls (48% vs 7%, p<0.001). Among influenza patients, there were significant correlations between CoQ10 levels and inflammatory markers such as IL-2, TNF-alpha and VEGF, but no correlation with IL-6, IL-10, VCAM or influenza severity of illness.

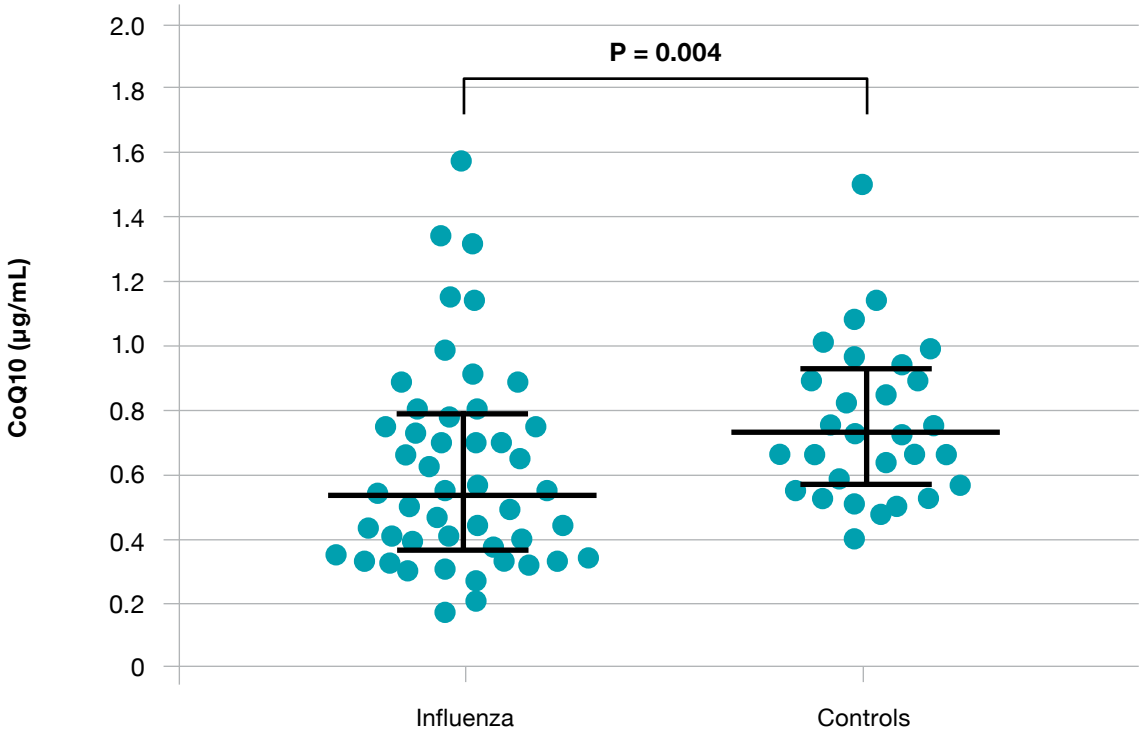


Figure 16. Box Plot of CoQ10 levels between patients with influenza and controls.

The relationship between total antioxidant capacity, CoQ10 and clinical outcomes in children with influenza

Viral influenza pneumonia negatively impacts the body in numerous ways, including the depletion of antioxidants and protective compounds such as ubiquinol, thus contributing to tissue damage and disease severity. To better understand this relationship, a study was conducted which evaluated the levels of total antioxidant capacity (TAC), CoQ10 and clinical outcomes in hospitalised children with pandemic influenza (H1N1), matched for age and sex with healthy children included as the control group.[119] Serum copper (Cu) and zinc (Zn) levels were also determined to evaluate any changes in oxidative stress enzyme activities depending on their cofactor concentrations.

Of the 65 children hospitalised (n=28 with H1N1, n=37 with seasonal influenza (SI)), those with H1N1 had significantly lower levels of TAC, CoQ10 and Zn, and those with seasonal influenza had significantly lower levels of TAC and Zn, as compared to the control group. CoQ10 levels were also found to be significantly decreased in children with H1N1 compared to the seasonal influenza group (p=0.003) **(Table 3).** A significant correlation was found between decreased CoQ10 levels and increased pulmonary involvement in children with H1N1, but not in those with SI **(Figure 17).**

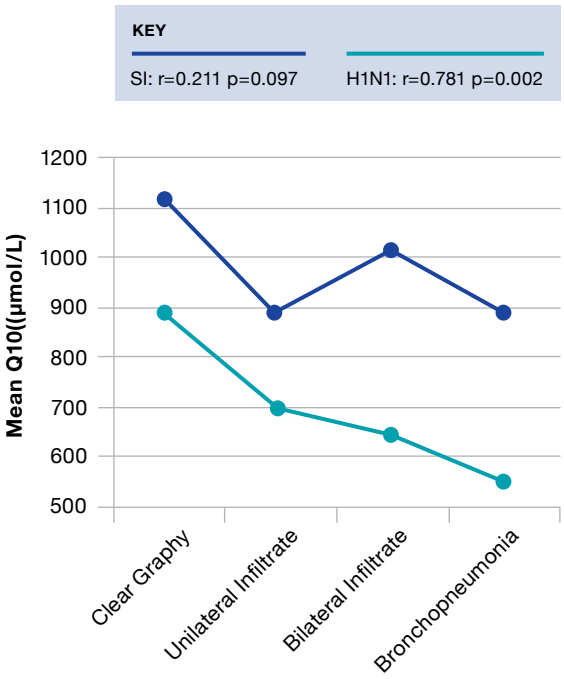


Figure 17. Mean CoQ10 levels were correlated with pneumonia severity (p=0.002) in H1N1 but not in SI (p=0.097).

	Controls (n=31)	SI (n=27)	H1N1 (n=28)	Difference P1	P2	P3
TAC (µmol H_2O_2Equiv./L)	1.64 ± 0.36	1.31 ± 0.27	1.01 ± 0.19	0.009	0.003	0.006
Q10 (µmol/L)	934 ± 217	1022 ± 199	752.2 ± 163	0.141	0.011	0.003
Cu (µg/dL)	136 ± 52	127 ± 37	150 ± 45	0.342	0.175	0.215
Zn (µg/dL)	92 ± 41	78 ± 34	69 ± 27	0.024	0.018	0.142

Table 3. Comparison of serum oxidative stress variables in studied groups (mean ± standard deviation)

Platelet mitochondrial function and CoQ10 levels are reduced in patients after COVID-19

'Post-COVID-19 Syndrome' or 'Long COVID' describes the persistence of symptoms for weeks or months after the acute phase of the infection has passed. The main symptoms experienced include general fatigue, muscle and joint pain, cough, loss of taste and smell, headaches, memory disturbances, poor sleep, mood disorders, and an increased sensitivity to sound and light.[116] In order to better understand the mechanism with which the SARS-CoV-2 virus effects mitochondrial dynamics and function, a study was conducted which assessed total CoQ10 levels, along with platelet mitochondrial respiration and oxidative phosphorylation in ten patients 4-7 weeks after overcoming COVID-19 infection and in 15 healthy individuals.[116]

The results of the study showed a significant reduction in whole blood (p=0.014) and plasma (p=0.034) CoQ10 levels in the post-COVID-19 group, as compared to the healthy controls **(Table 4)**. Mitochondrial respiration and oxidative phosphorylation, both associated with ATP production, were also reduced in platelets of post-COVID-19 individuals. These findings indicate that a deficit of CoQ10 may partially block electron transfer in the respiratory chain, resulting in reduced ATP production after COVID-19 infection. As such, strategies to target mitochondrial bioenergetics and antioxidant defence, such as supplementing with ubiquinol, will play an important role in improving mitochondrial health and promoting a faster recovery in individuals after COVID-19.

	Control	Post-COVID-19	p	% of control
$CoQ10_{-TOTAL}$ Platelets (pmol.10^{-9} cells)	84.1 ± 5.3	58.9 ± 3.60	0.002	70.0
Blood (µmol.L^{-1})	0.313 ± 0.020	0.217 ± 0.030	0.014	69.1
Plasma (µmol.L^{-1})	0.516 ± 0.030	0.394 ± 0.043	0.034	76.3
TBARS (µmol.L^{-1})	5.035 ± 0.213	4.619 ± 0.225	0.2	91.7

Table 4. Endogenous CoQ10 (total) and thiobarbituric acid reactive substances (TRABS – a parameter of oxidative stress)

Do cellular ubiquinol levels hold the secret to healthier aging?

With increasing age and prolonged stress due to lifestyle, diet or environmental factors, the ability to convert ubiquinone to ubiquinol declines and our natural ubiquinol levels become depleted.[3,52] For example, studies show that endogenous production of ubiquinol starts to decrease after the age of 20 years and, by 80 years of age, the myocardial concentration of ubiquinol has reduced by around half.[61]

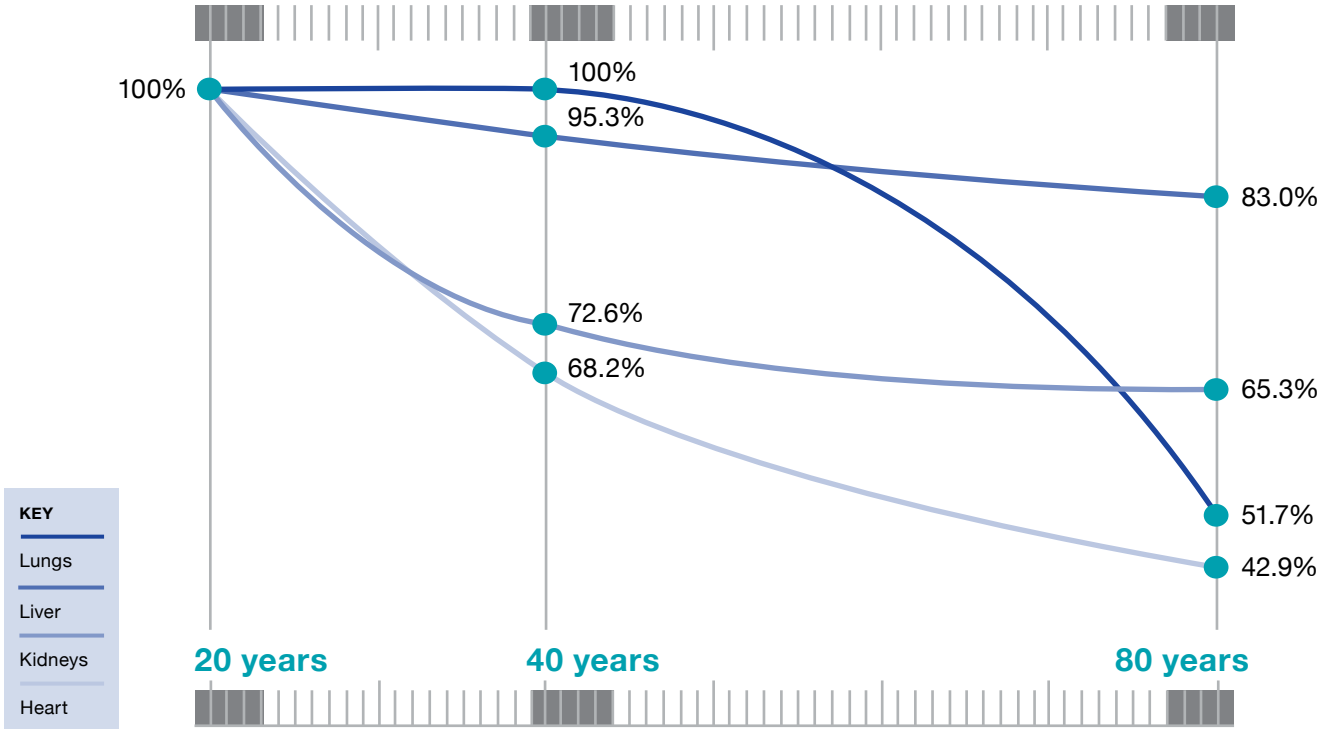


Figure 18: Agro FOOD Industry Hi Tech- March/April2013-Vol.24(2) [120]

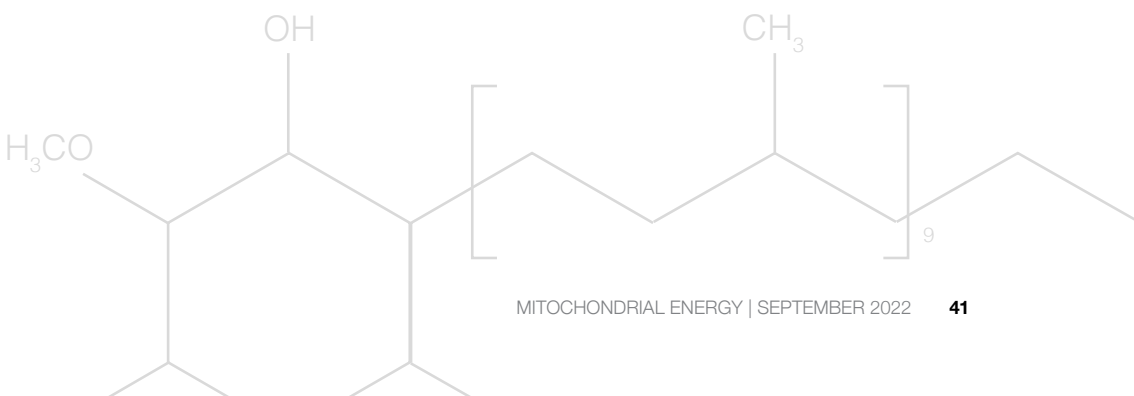
In addition to decreased endogenous production of ubiquinol with age, the free radical activity and oxidative stress that occurs in our body from normal metabolism, even in healthy individuals, increases as we get older, creating an imbalance between ROS production and antioxidant defences.[4] This combination of increased oxidative stress, low-level systemic inflammation and reduced antioxidant capacity are major drivers in accelerated ageing and age-related disease development.[52] Given the important role of oxidative stress in the pathogenesis of many clinical conditions associated with aging, antioxidant therapy has been investigated as a means to positively affect the outcome of several disease states.[121]

Low levels of ubiquinol have been found in older people and in those with type 2 diabetes, impaired immunity, cardiovascular, neurological and liver diseases. This can contribute to fatigue due to reduced cellular energy production and increased oxidative stress and damage. The risk of developing any of these conditions may be reduced by quenching oxidative stress and supporting mitochondrial function through regular ubiquinol supplementation.[52, 122]

It has been reported that plasma ubiquinol levels are significantly higher in healthy individuals of advanced age than in elderly bedridden individuals, and that the risk of dementia is reduced approximately by half in individuals having high blood levels of ubiquinol.[123] Ubiquinol supplementation has been proposed as a strategy to slow down skeletal muscle senescence and improve the quality of life in the elderly.[45]

Older individuals may have decreased ubiquinol levels and an impaired ability to efficiently convert ubiquinone to ubiquinol due to:[52]

- *Increased metabolic demand*
- *Disease*
- *Oxidative stress*
- *Insufficient ubiquinol intake*
- *Deficiency of factors required for biosynthesis and conversion*
- *Gene mutation*
- *The use of statin medication*



6

ABOUT THE AUTHORS

Narelle Cooke

Narelle is a degree qualified clinical Naturopath, Nutritionist, and Herbalist for both people and pets based in Sydney Australia, where she operates her own private wellness clinic 'Natural Health and Nutrition'. Narelle is also the founder and Managing Director of the canine nutritional supplement range CanineCeuticals.
Narelle began her career over 25 years ago as a research pathologist in the agricultural industry, before moving on to work as a Regulatory Affairs Associate for a large international agrochemical company. During this time, Narelle developed a deep, first-hand understanding of the effect that pathogens and environmental toxins have on our food, our bodies and consequently, our health. It was this knowledge that motivated Narelle to commence her studies in natural medicine. More recently, Narelle worked for several years as a Research Officer and Technical Writer for an Australian healthcare company, while also conducting contract technical writing for other agencies within the healthcare sector. Each of these roles required Narelle to identify, assess, critically evaluate, synthesis and effectively communicate scientific and clinical information to a broad audience base, including consumers and healthcare practitioners.

Being a lifelong dog-owner and currently meeting the demands of three French Bulldogs, two German Shepherds, a Rottweiler and a Burmese cat, Narelle is as passionate about the health and wellbeing of our pets as she is about their owners. It was the strong desire to see her own pets live their longest and best lives that led her to hours of additional study and formal qualifications in natural animal health and nutrition.

Narelle is now passionate about educating both pet owners and industry healthcare professionals about the importance of nutrition and targeted supplementation for optimal health outcomes.

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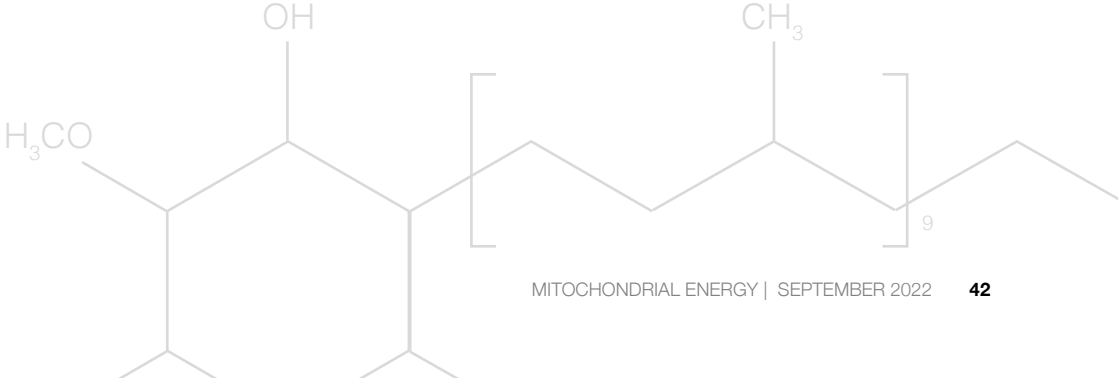


Gerald Quigley

Gerald is a Pharmacist based in Melbourne. He is a media health commentator heard each week on many radio stations across Australia.

He is a regular weekly guest on Australia Overnight, heard across the Nine Radio network and syndicated stations each Tuesday morning. He is a regular guest on 6PR Perth on Saturday evenings.

Additionally, he is co-host of the House of Wellness radio program heard each Sunday on the Nine Radio Network live across Australia, through 3AW Melbourne, 2GB Sydney, 4CA Brisbane, 5aa Adelaide and 6PR Perth. Gerald is a regular guest on House of Wellness TV seen on the Seven Network across Australia each week.

He has lectured in Drug & Integrative Pharmacology to 3rd Year students at the Southern School of Natural Therapies, part of the Torrens University Group, in Melbourne. Gerald has also published a textbook on the benefits of Olive Leaf Extract. Gerald is a Fellow of the Naturopaths and Herbalists Association of Australia and Fellow of the Australian Natural Therapists Association.

Gerald's passion is to empower each person to make sensible health decisions, and to continually maintain and improve their quality of life, especially as they age. Gerald reinforces our rediscovering of the ability to understand wellness, the role of food choices, and aging well – all of which are aspects of vitality fundamental to our future.

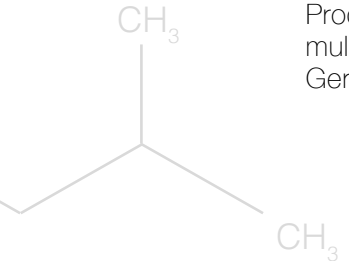
Product development and associated for mulations are an important interest, where Gerald seeks the most effective outcome for our patients. Medications can be lifesaving, but today's consumer is well educated and is aware of adverse effect profiles. They seek effective options with minimal risk.

In Gerald's view, inflammation is the key underlying driver of chronic disease which in turn reduces quality-of-life. The "illness system" treats symptoms. Most patients can live "with" a health issue if they have been empowered with information and options, rather than being "dominated by" that condition at every stage.

Gerald is excited to join Neurotech International at this very important time, based on current research which offers improvements to the quality-of-life of many people. From key developments in a current Paediatric Autism Spectrum Disorder Study at Monash Children's Hospital, to the control of pain at every level.

Gerald considers this appointment as a privilege in his passionate commitments to patient care.

Gerald Quigley
Pharmacist



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