



& succinate.<sup>3</sup>

5 6.5

3.0

2.5

2.0



**Ubiquinone:** The fully oxidized form of CoQ10 is ubiquinone-10, or simply ubiquinone, and is often represented as "Q". Ubiquinone is a required coenzyme of the Q cycle and is also involved in glycolysis and lipolysis.<sup>39,25</sup> A full representation shows all 10 ubiquinone isoprenyl subunits. The chemical structure may be represented by showing the oxidized quinone head attached to a bracketed isoprenyl subunit with a 10 subscript.

may be represented by showing the reduced hydroquinol (reduced quinone) head attached to a bracketed isoprenyl subunit with a 10 subscript.

## **Predominance of Ubiquinol**



Ubiquinol is the predominant form of CoQ10 in the human body.<sup>43</sup> In adults, 92% to 98% of total CoQ10 is in its reduced form as ubiquinol, while the percentage may be from 93% to 100% for people less than 18 years of age.<sup>43</sup> Tissues with a higher percentage of ubiquinol than ubiquinone include the kidney, liver, muscles, pancreas, spleen, thyroid, intestines and colon.<sup>14,38</sup> A little less than 50% of heart CoQ10 is ubiquinol, while slightly less than 25% of brain and lung CoQ10 is ubiquinol. It should be noted that even though the percentage of ubiquinol to ubiquinone in the heart is less than 50%, the amount of ubiquinol per gram of heart tissue is actually higher in the heart than the amount found in other tissues.<sup>14</sup>

As the predominant form of CoQ10 in the human body, ubiquinol can be regenerated at the cellular level by various enzymes. This regeneration of ubiquinol from the oxidized form ubiquinone is essential to the maintenance of its antioxidant function.<sup>42</sup> Enzymes involved in this regenerative process include lipoamide dehydrogenase, glutathione reductase, and thioredoxin reductase.<sup>42,44,45</sup> All three enzymes can also reduce lipoic acid to its antioxidant form dihydrolipoic acid, which can reduce ubiquinone to ubiquinol.<sup>14,46</sup> Another enzyme involved in reducing ubiquinone is DT-diaphorase, which also protects ubiquinol from being oxidized.<sup>47,48</sup>

# COENZYME Q10 Ubiquinone-10 and Ubiquinol-10

# Nano-colloid delivery system enhances absorption & increases bioavailability



The Q Cycle is a series of reactions within the electron transport chain that involve sequential oxidation and reduction of the lipophilic electron carrier, ubiquinol-ubiquinone (Coenzyme Q) in a cyclical fashion that ultimately results in the pumping of protons across a lipid bilayer, such as a cell membrane or the membrane of a cell organelle.<sup>14,39</sup> The citric acid cycle, not shown in this graphic, donates electrons to the Q-cycle through NADH

The cyclical oxidation and reduction of CoQ10 is required for oxidative phosphorylation, which is the metabolic pathway that uses energy released by the oxidation/reduction of nutrients to produce adenosine triphosphate (ATP), the molecule required for intracellular energy transfer.<sup>39</sup> More specifically, CoQ10 interacts with a series of protein complexes within mitochondria that act as enzymes to create a proton gradient across the inner mitochondrial membrane into the matrix. The concentration gradient drives ATP synthase to convert ADP to ATP.<sup>40,49,50</sup>

While intracellular transport of CoQ10 may be ATP dependant, ATP synthase (not shown in this graph) does not depend on CoQ10 to function.<sup>14</sup> The protein three complexes that depend upon the Q Cyle include Complex, I, Complex II & Complex III, which are three of the four complexes in the electron transport chain.<sup>14,39,40,49,50</sup> Though not directly used by ATP synthase, ubiquinone and ubiquinol both drive the electron transport chain that creates the protonic gradient which is used by ATP synthase to produce ATP.

The Q Cycle also supports the function of glyceraldehyde 3-phosphate dehydrogenase (G3PDH), a glycolysis enzyme required to convert glucose to create energy.<sup>39</sup> In addition, the Q Cycle supports the function of **Thermogenin (UCP1)**, an uncoupling protein in the mitochondrial membrane that removes protons from fatty acids in the intermembrane space and moves the protons to the matrix to create heat instead of converting ADP to ATP.<sup>24</sup> Thermogenin requires oxidized CoQ10 (ubiquinone) to subtract H+ from fatty acids and deliver them to the H+ acceptor group of UCP1.<sup>25,26</sup> Proper thermogenin function is required for lipolysis and optimal fatty acid metabolism, healthy body weight and ideal utilization of glucose. Reduction of Ubiquinone to Ubiquinol takes place in Complex I, Complex II, G3PDH & UPC1 Oxidation of Ubiquinol to Ubiquinone takes place in Complex III

# **Bioavailability of CoQ10**



Serum Myocardium Mitochondria

taking CoQ10 with food only causes a very modest increase in bioavailability.<sup>53</sup>

As a fat soluble bioactive molecule, CoQ10 has pronounced hydrophobic & lipophilic properties

water solubility of Class II BCS bioactive compounds traditionally limits their bioavailability.<sup>52</sup> Even

and therefore exhibits poor water solubility but high membrane permeability, which makes

CoQ10 a class II compound in the Biopharmaceutical Classification System (BCS).<sup>51</sup> The poor

Increasing bioavailability has a direct affect on the **tissue and** mitochondrial levels of CoQ10. A 3.8 times increase in serum levels(ug/ mu resulted in a 2.5 times increase in myocardial tissue(ug/g) CoQ10 levels and a 2.4 times increase in the CoQ10 levels of cardiac mitochondrial protein(ug/mg).54

nano-colloidal formulation

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 Differences in Bioavailability of Different Ubiquinone Formulations

Clinical outcomes are dependent on increased bioavailability. Increased clinical improvement in congestive heart failure (CHF) patients is only seen with plasma CoQ10 levels of at least 2.5 ug/ml.<sup>5</sup> Therapeutic plasma levels in CHF are now considered to be greater than 3.5 ug/ml.<sup>56,57</sup> The greatest benefit for Parkinson disease patients was seen at CoQ10 dosages that achieved plasma CoQ10 levels of at least 3.5 ug/ml.<sup>58</sup> Similarly, the progressive spread of breast disease to the liver was decreased when blood levels of CoQ10 were maintained in the 3.34 to 3.77 range.<sup>59</sup> As the "Difference in Bioavailability" graph indicates, increased bioavailability is critical to achieve and maintain these levels.

As the "Difference in Bioavailability" graph indicates, there is a significant difference in bioavailability between various brands and formulations of CoQ10 supplements.<sup>1,61</sup> Suspension, solubilizates, oil based formulations and even micro-emulsions are not able to achieve and maintain therapeutic levels of CoQ10 that are readily achieved by nano-colloidal delivery systems.<sup>51,53</sup> A nano-colloidal delivery system is a lipid based formulation that upon contact with an aqueous fluid self-assembles into millions of tiny droplets that are in cryo-electron micrograph of

the size range of less than and around 100 nm in diameter. A nano-colloidal CoQ10 delivery system has been developed, which is able to significantly improve the bioavailability of CoQ10.<sup>60,61</sup> This nano-colloidal CoQ10 delivery system releases nano droplets with a well defined average diameter of 70 to 75 nm, as observed in the cryo-electron micrograph of the nano-colloidal formulation used in the above graph.<sup>51,62-65</sup>

# Nano-Colloid Delivery of CoQ10

Mucus maintains an unstirred water layer adjacent to the intestinal epithelial cells (enterocytes) despite the shearing actions of intestinal peristalsis.<sup>66</sup> The tenacious properties of mucus prevent most particles from penetrating to the epithelial surface, including some nano-particles.51,67

The nano-colloidal CoQ10 delivery system is able to effectively increase bioavailability of CoQ10 by penetrating the mucus mesh and easily diffusing across the unstirred water layer.<sup>51</sup> The mucus mesh barrier can be crossed by the fluid nano-colloid CoQ10 droplets with sizes of less than 75 nm, that are created with precise ratios of food grade nonionic emulsifiers and dietary triglycerides / fatty acids.<sup>51,62</sup> Due to the nonionic nature of the nano-colloid CoQ10 droplets, they do not interact with mucin and are capable of diffusing freely through the mucus matrix.<sup>68</sup> Penetration of the nano-colloidal CoQ10 droplets through the mucus mesh and across the unstirred water layer delivers CoQ10 to the surface of the enterocytes.

Once the nano-colloid delivers CoQ10 to the surface of the enterocyte, the high membrane permeability of CoQ10 allows passive diffusion of CoQ10 molecule into the enterocytes.<sup>51,52</sup> The binding and transfer of the lipophilic CoQ10 molecules between the intracellular lipid surfaces, and its transport through the enterocyte, is mediated by proteins such as saposin B, a glycoprotein that also binds and transfers gamma tocopherol, other lipids and phospholipids. The enterocytes incorporate CoQ10 into chylomicrons that are carried to the lateral surface of the enterocytes for exocytosis into the extracellular space, which drains into lymph vessels and is then taken up by liver cells and associated with lipoproteins such as VLDL & LDL to be distributed to tissues throughout the body.<sup>72-74</sup>

> Nano-colloid droplets passing throug mucin matrix in unstirred laye

Ubiquinol is the predominant form of CoQ10 in the human body and should make up at least 92% to 93% of the total plasma CoQ10 concentration in adults, such that the ratio of **ubiquinol** to ubiquinone can be as high as 50 to 1.43,75 The ratio of ubiquinol to ubiquinone can change with age as well as various disease states.<sup>43,77,78</sup> Assessing the ubiquinol to ubiquinone ratio may be used for both a biomarker of condition associated oxidative stress and as a biomarker of aging.<sup>78-80</sup>

Age Associated Decline in Ubiquinol to Ubiquinone Ratio It is now widely recognized that during aging there is a pro-oxidizing shift in the cellular redox state, accompanied by an accrual of the amounts of molecules damaged by oxidative stress, and subsequent progression of senescence.<sup>76</sup> As a powerful lipophilic antioxidant, ubiquinol plays a critical role in decreasing oxidative stress. However, the ratio of reduced CoQ10 (ubiquinol) to oxidized CoQ10 (ubiquinone) can adversely change with age.<sup>43,77</sup> The age associated increase in oxidative stress can best be demonstrated by observing the age dependent drop in the ubiquinol to ubiquinone ratio; a phenomenon considered evidence of increased oxidative stress in both aging and in disease states.<sup>43,76-79</sup> While the ubiquinol to ubiquinone ratio only drops slightly between younger children and older children, the average drop increases in adulthood and continues with age.43,77



Since its discovery in 1957, coenzyme Q10 (CoQ10) has been the subject of about 9,000 published studies, with over 2,500 of those studies focused on the direct affect that ubiquinone and/or ubiquinol have on human health and disease. Almost 200 papers focus on the role that ubiquinone/ ubiquinol has on congestive heart failure. While ubiquinone and ubiquinol both play very significant roles in antioxidant, bioenergetics, cell signaling and gene expression which affect the health and function of every body system, it is notable that ubiquinol is the preeminent antioxidant in the human body which is why ubiquinone/ubiquinol may have applications in so many health conditions.

CoQ10 levels are decreased in both the plasma and the brain tissue in patients with neurological conditions associated with progressive loss of **dopaminergic neurons** in the substantia nigra. These, and other neuronal changes cause complex and variable motor and nonmotor symptoms. Supplementation with CoQ10 (with **ubiquinol** producing the largest increases in plasma concentrations) may provide neuroprotection and decrease dopaminergic dysfunction by supporting proper mitochondrial function. CoQ10 may also support supranuclear mitochondrial function in other neurological conditions.<sup>90,104-107</sup>

CoQ10 levels in the **retina** can decline by approximately 40% with age, which may be linked to the progressive **degeneration** of the **macula** (the central retina which provides vision for fine work and reading).<sup>91</sup> The antioxidant properties of CoQ10 are considered to be the mechanism of action in retinal protection.<sup>92,93</sup>

CoQ10 can support healthy sight by preserving the function of the **retinal ganglion** cells that may be compromised by high **intraocular pressure**.<sup>94-96</sup> CoQ10 may also provide cardio-protection when beta-blockers are used to address high intraocular pressure.<sup>97</sup>

CoQ10 levels are lower in both the serum and the heart tissue of patients with heart muscle disorders with decreased heart function.<sup>98</sup> Ubiquinol was able to dramatically increase plasma CoQ10 levels in patients with decreased heart function, even after supplementation with ubiquinone failed to reach therapeutic goals.<sup>57</sup> The **ubiquinol** intake was associated with improvement in **ejection fraction**, a measure of heart function.<sup>99</sup>

**Ubiquinol** percentage is lower in hyperlipidemic patients that have high **blood pressure** compared to subjects without high blood pressure.<sup>86</sup> CoQ10 supplementation supports the body's natural blood pressure regulatory mechanisms with a normalizing affect on both systolic and diastolic values.<sup>100</sup> CoQ10 may also normalize the elevated **blood pressure** associated with

Genetic CoQ10 deficiency conditions that affect nerve, muscle, metabolic syndrome by attenuating the increase of oxidative stress kidney and heart function may be due to mutations in ubiquinone and nitrative stress markers and inflammatory markers typically seen in biosynthetic genes or mutations in genes not directly related to CoQ10 that syndrome.<sup>101</sup> biosynthesis.<sup>35</sup> They have been associated with autosomal recessive Ubiquinol percentage of total CoQ10 is significantly lower in the neurological disorders that are responsive to CoQ10 supplementation.<sup>130</sup> presence of metabolic conditions accompanied by high and very These conditions typically manifest during infancy and childhood, but high **blood sugar** levels, such that the very high **blood sugar** levels, such some patients have presented with adult-onset cerebellar ataxia or that patients with very high blood sugar levels may have ubiquinol myopathy.<sup>36,130,131</sup> A significantly lower **ubiquinol** percentage and total percentages as low as 24% in males and 29% in females.<sup>79</sup> The change CoQ10 observed in children with trisomy 21 (Down syndrome), were both in **ubiquinol** %, reveals increased **oxidative stress** which may contribute increased twelve fold, with a majority of them achieving normal ratios, to increased risk of cardiovascular disorders.<sup>102,103</sup> when supplemented with ubiquinol.83

# Condition Associated Superiority of Ubiquinol for Improving Biomarkers of Health

Ubiquinol showed superiority over ubiquinone for improvement of biomarkers of cardiac function in a group of patients with heart muscle disorders. When patients were switched from average daily dosage of 450 mg of ubiquinone to 580 mg of ubiquinol, plasma levels of CoQ10 increased from an average of 1.6 ug/ml to 6.5 ug/ml, revealing a four-fold increase in levels with only a 28% increase in dosage.<sup>57</sup> Their average ejection fraction improved from an average of 22% to 39%. On ubiquinone, their average NYHA classification was IV (severe limitations with symptoms at rest), but after switching to ubiquinol they improved to NYHA Class II (slight limitations during ordinary activity and mild symptoms).<sup>57</sup> The increased intestinal edema that is associated with diminished cardiac function may be responsible for the decreased ubiquinone absorption seen in these patients.<sup>57,132,133</sup>

. .... LUMEN UNSTIRRED LAYER 80880 00 ENTEROCYTE \*\* \*\*\*\*\* chylomicrons

● ● [ 75 nm

000

00000

000000

lymph vessels





# **Physiological Indications for Ubiquinol**



Age Related Drop in Ubiquinol : Ubiquinone Ratio Condition Associated Decline of Ubiquinol

The percentage of ubiquinol to total CoQ10 (ubiquinol %) is another method of assessing CoQ10 function. Health conditions often have a significant effect on the percentage of ubiquinol (ubiquinol %). Subjects (60) with fasting glucose (FG) less than 99 mg/dl had normal ubiquinol % (male 93%, female 95%), while subjects with and FG of 100 to124 had a significant drop of ubiquinol % (male 43%, female 41%), and subjects with Type 2 diabetes (and FG >124) were noted has to have severely low ubiquinol % (male 24%, female 29%).<sup>103</sup> The lower ubiquinol % levels are recognized as a sign of increased oxidative stress, which may be responsible for the increased observance of vascular and micro-vascular co-morbidity seen in Type 2 diabetes.<sup>79</sup> It is the low percentage of ubiquinol levels, not the total CoQ10 levels, that are recognized as clinically relevant in a number of conditions that have increased oxidative stress as a component of their pathology, including various neurological, cardiovascular, pulmonary, genetic mitochondrial, and hepatic disorders, as well as the dysglycemic disorders.<sup>57,78-8</sup>

# Research & Observations on CoQ10

CoQ10 may have a beneficial effect on neurological conditions marked by progressive, irreversible degeneration of the brain cells and severe loss of memory by supporting healthy mitochondrial function which resists betaamyloid production caused by oxidative stress.<sup>88-90</sup> Ubiquinol percentage may be considerably lower in some neurological conditions that involve degeneration of upper and lower **motor neurons**. CoQ10 may improve the mitochondrial function in these cases.<sup>82,108</sup>

> CoQ10 reduces **cochlear oxidative stress** induced by acoustic overstimulation and can preserve cochlear hair cell by promoting recovery from damage in **auditory** hairs as well as preventing mitochondrial damage.<sup>110-112</sup> Chronic **ringing** in the **ears** may be improved if low CoQ10 levels are increased by supplementation.<sup>109</sup>

CoQ10 can support the health of the **periodontium** (the tissues that surround and support the teeth), most probably by decreasing the oxidative stress in those tissues.<sup>113-115</sup>

centage is significantly lower in pulmonary conditions which have some degree of chronic obstruction.<sup>78</sup> CoQ10 can improve muscular energy metabolism when there is low blood oxygen levels at rest and/or during exercise.<sup>116</sup> Chronic **inflammatory** conditions of the **respiratory system** 

are associated with lower concentrations of CoQ10 with a concomitant antioxidant imbalance that may be ameliorated with CoQ10 supplementation.<sup>117</sup> CoQ10 supplementation may also support a decreased dependency on corticosteroids in chronic inflammatory conditions of the respiratory system.<sup>118</sup>

**piquinol percentage** is lower in seminal fluid of idiopathically infertile males, which is believed to be due to the impaired function of protective antioxidant activity.<sup>119-121</sup>

Clinical trials have demonstrated a considerable variation in the decrease of CoQ10 levels on patients taking different HMG-CoA reductase inhibitors (statins), ranging from 26% to 57% drops of total CoQ10.<sup>122-125</sup> It has also been observed that **ubiquinol** levels may drop by 20% to 43%.<sup>123,126</sup> Genetic predisposition may be associated with the intolerance and risks associated with HMG-CoA reductase inhibitor use.<sup>128,129</sup>

# Improvement of Biomarkers

