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# Coenzyme Q10 deficiency can be expected to compromise Sirt1 activity

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## ABSTRACT

For reasons that remain unclear, endogenous synthesis and tissue levels of coenzyme Q10 (CoQ10) tend to decline with increasing age in at least some tissues. When CoQ10 levels are sufficiently low, this compromises the efficiency of the mitochondrial electron transport chain, such that production of superoxide by site 2 increases and the rate of adenosine triphosphate production declines. Moreover, CoQ10 deficiency can be expected to decrease activities of Sirt1 and Sirt3 deacetylases, believed to be key determinants of health span. Reduction of the cytoplasmic and mitochondrial $NAD^+$/NADH ratio consequent to CoQ10 deficit can be expected to decrease the activity of these deacetylases by lessening availability of their obligate substrate $NAD^+$. The increased oxidant production induced by CoQ10 deficiency can decrease the stability of Sirt1 protein by complementary mechanisms. And CoQ10 deficiency has also been found to lower mRNA expression of Sirt1. An analysis of the roles of Sirt1/Sirt3 in modulation of cellular function helps to rationalise clinical benefits of CoQ10 supplementation reported in heart failure, hypertension, non-alcoholic fatty liver disease, metabolic syndrome and periodontal disease. Hence, correction of CoQ10 deficiency joins a growing list of measures that have potential for amplifying health protective Sirt1/Sirt3 activities.

## SUBOPTIMAL COENZYME Q10 (COQ10) STATUS MAY DIMINISH SIRT1 ACTIVITY BY MULTIPLE MECHANISMS

The physiologically essential cofactor CoQ10 functions to transport elections from site 1 and 2 in the mitochondrial electron transport chain (ETC) to site 3. Although CoQ10 can be synthesised within mitochondria, certain rare genetic variants of genes required for this synthesis are associated with effective CoQ10 deficiency and clinical syndromes.[1 2] However, even in the majority of individuals lacking such variants, suboptimal CoQ10 levels—impairing the efficiency of the ETC—may develop in specific tissues with ageing.[3 4] CoQ10 deficiency may be said to exist when this inefficiency leads to an increased backup of electrons at sites 1 and 2; this has been shown to increase superoxide generation at site 2 and is also associated with reduced efficiency of adenosine triphosphate (ATP) generation.[5] This increased production of reactive oxygen species (ROS) and associated reduction in ATP levels can evidently compromise the function of affected tissues.

Moreover, there is reason to believe that Sirt1 and Sirt3 activity will be impaired in CoQ10-deficient cells. First, their activities will be decreased by the decline in $NAD^+$/NADH ratio, both in the cytoplasm and in mitochondria, that results from the backup of electrons in the proximal portion of the ETC.[6 7]

Second, the elevation of ROS associated with such deficiency can be expected to decrease Sirt1 protein expression by increasing its proteasomal degradation. Oxidant stress, in part via activation of apoptosis signal-regulating kinase 1, tends to promote activation of the stress-activated mitogen activated protein (MAP) kinases: c-Jun N-terminal kinase (JNK) and p38.[8–10] The former confers a phosphorylation on Ser47 of Sirt1 that prepares it for ubiquitination and subsequent proteasomal degradation.[11] This effect is however opposed by the widely expressed deubiquitinase USP22.[12–14] Transcription of the USP22 gene is inhibited by binding of Sp1 transcription factor to the proximal promoter of this gene and phosphorylation of Sp1 by p38 MAP kinase enables Sp1 to bind to this promoter.[15–17] Hence, p38 activation decreases synthesis of an enzyme that impedes the proteasomal degradation of Sirt1. In this way, the activation of JNK and p38 stemming from CoQ10 deficiency can collaborate to accelerate the proteasomal destruction of Sirt1.

Third, the synthesis of Sirt3—a key factor in control of oxidative stress within the mitochondrial matrix[18–21]—is promoted by Sirt1 activity, and hence will be compromised by CoQ10 deficiency. Sirt3 synthesis is driven by a complex between PPARγ coactivator-1α (PGC-1α) and the transcription factor estrogen-related receptor-α; as is well known, Sirt1 activity plays a key role in both the activation and the expression of PGC-1α.[22–24]

Finally, there is evidence that CoQ10 status can regulate Sirt1 expression at the mRNA level, at least in the context of diabetes. In rats rendered diabetic by streptozotocin administration, hepatic Sirt1 mRNA declines; this effect is reversed by CoQ10 administration.[25] The mechanistic basis for this effect remains unclear. Certain microRNAs that downregulate Sirt1 are reported to be upregulated in diabetic rodents and in cell lines exposed to hyperglycaemic.[26–29]

## PHYSIOLOGICAL IMPLICATIONS OF DIMINISHED SIRT1/SIRT3 ACTIVITY

The consequences of decreased Sirt1/Sirt3 activity can include:

- Decreased mitophagy and mitochondrial biogenesis—effects which can evidently amplify the oxidant stress and diminished ATP production associated with CoQ10 deficiency.[30–32] CoQ10 deficiency can however be associated with increased mitophagy, likely owing to oxidant-mediated damage to the mitochondrial inner membrane detected by the Pink/Parkin system.[33 34] In other studies, added CoQ10 has enhanced mitophagy, possibly owing to enhanced Sirt1/Sirt3 activity.[35 36]
- Increased activity of the proinflammatory transcription factor nuclear factor kappa beta (NF-kappaB), the activity of which Sirt1 represses via deacetylation.[37 38]
- Decreased activity of the Nrf2 transcription factor—activated by Sirt1-mediated deacetylation[37 38]—which promotes expression of a range of antioxidant enzymes and also boosts synthesis of the key intracellular antioxidant glutathione.[39]
- Decreased activation of AMP-activated kinase (AMPK), reflecting the fact that Sirt1 activity stabilises and promotes appropriate intracellular localisation of its upstream activating kinase LKB1.[40] AMPK promotes autophagy;[41–43] it also enhances utilisation of free fatty acids as fuel, an effect which opposes development of obesity and lipotoxicity.[44]
- Decreased synthesis of the KLF2 transcription factor.[45 46] Within endothelial cells, KLF2 exerts important anti-inflammatory and antithrombotic effects, and also promotes transcription of endothelial nitric oxide synthase (eNOS), of vital importance to healthful endothelial function.[47 48]
- Decreased activity of eNOS, as Sirt1-mediated deacetylation of this enzyme boosts its activity.[49]
- Upregulation of apoptosis and senescence, owing to the fact that Sirt1 promotes efficient DNA repair, while inhibiting the proapoptotic activity of p53 and FOXO factors by deacetylating them.[50–54]
- Increased hepatic de novo lipogenesis, owing to the fact that Sirt1 activity, via deacetylation of the transcription factor sterol response element binding protein-1c (SREBP-1c), decreases the expression of enzymes catalysing lipogenesis.[55]
- Decreased adipocyte production of adiponectin. A complex of FOXO1 and C/enhancer-binding protein a forms on the promoter of the adiponectin gene to drive its transcription; deacetylation of FOXO1 by Sirt1 is required for formation of this nuclear complex.[56–58]

## ENHANCED SIRT1 ACTIVITY MAY EXPLAIN SOME BENEFITS OF COQ10 SUPPLEMENTATION

The implications of cellular CoQ10 deficiency can thus extend far beyond ATP deficit and increased mitochondrial ROS generation. The clinical consequence will hinge on the specific types of cells in which CoQ10 is deficient.

If we consider clinical conditions in which supplemental CoQ10 has been most often employed with some worthwhile efficacy—congestive heart failure, hypertension, and periodontal disease[59–64]—measures which positively modulate Sirt1 activity have been shown to have a beneficial influence in rodent models of these syndromes, whereas the converse is also true.[65–73]

The ability of Sirt1 to boost AMPK activity, while diminishing that of SREBP-1c and NF-kappaB, suggests that CoQ10 supplementation might sometimes be useful in management of non-alcoholic fatty liver disease—a prediction consistent with rodent studies and initial clinical studies evaluating CoQ10 in this disorder.[74–77]

A recent meta-analysis of CoQ10 supplementation in patients with metabolic syndrome reveals that CoQ10 enhances plasma adiponectin levels while decreasing C reactive protein (CRP), fasting glucose and glycated haemoglobin levels.[78] A key mediator of this effect may be adipocytes, as mitochondrial levels of CoQ10 have been found to be lower in insulin-resistant mouse adipocytes and in adipose tissue from insulin-resistant humans.[5] Also, Sirt1 depletion of adipocytes has been shown to sensitise mice to diet-induced insulin resistance; this may reflect the fact that, via anti-inflammatory effects on adipocyte cytokine production, Sirt1 activity lessens the recruitment and M1 polarisation of macrophages in adipose tissue.[79] This effect might be expected to moderate CRP production while aiding maintenance of peripheral insulin sensitivity and glycaemic control. Mitochondrial oxidant production in CoQ10-deficient adipocytes can itself promote adipocyte insulin resistance, but lack of the antioxidant impact of Sirt1 could be expected to potentiate this effect.[5]

## REGULATION OF COQ10 LEVELS: MORE QUESTIONS THAN ANSWERS

Presumably, CoQ10 will be beneficial primarily in circumstances where mitochondrial levels of CoQ10 have declined to the point where they are rate limiting for ETC electron transport. Why does this happen in specific tissues in specific disorders? Although the multiple mitochondrial enzymes required for human CoQ10 synthesis are being characterised, the mechanisms regulating

CoQ10 synthesis are still poorly understood.[80] In ageing rodents, age-related declines in CoQ10 have been observed in heart, kidney and skeletal muscle, whereas hepatic levels increase.[81] In humans, heart levels of CoQ10 peak at about age 20 years and decline by about 50% at age 80 years.[82] In heart failure patients, heart levels of CoQ10 decline as the stage of heart failure worsens—do the cellular perturbations associated with heart failure compromise CoQ10 synthesis?[83] And do signals that promote mitochondrial biogenesis likewise promote CoQ10 synthesis?

One report is of particular interest: PPARα agonists were shown to boost CoQ10 levels in the liver, kidney and heart of mice via induction of a number of enzymes required for CoQ10 synthesis.[84] Since the xanthophyll carotenoid astaxanthin has been found to function as a PPARα agonist, it is conceivable that astaxanthin supplementation—which could also be expected to protect the mitochondrial ETC from oxidative damage via its oxidant scavenging activity[85]—could be useful for maintaining healthful cellular levels of CoQ10.[86–88] PPARα activity also promotes expression of mitochondrial enzymes required for fatty acid oxidation and ketogenesis.[89 90]

Treatment with statins or bisphosphonates interferes with CoQ10 synthesis by suppressing production of isoprenyl group precursors.[91 92] Whether CoQ10 supplementation of elderly people treated with these drugs might improve their long-term health outcomes is not yet clear; however, CoQ10 deficiency does not appear to be the primary mediator of statin-induced myopathy.[84]

Additional nutraceuticals with practical potential for boosting Sirt1 activity, as recently reviewed, include ferulic acid, melatonin, N1-methylnicotinamide, urolithin A, berberine and nicotinamide riboside.[93–100] Curiously, ferulic acid may mediate much of the health benefit associated with ingestion of unrefined whole grains and anthocyanin-rich fruits and vegetables, whereas urolithin A may mediate the protection afforded by ellagitannins present in pomegranates and other foods.[101–103]

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