openheart

Coenzyme Q10 deficiency can be expected to compromise Sirt1 activity

James J DiNicolantonio [1], Mark F McCarty,[2] James H O'Keefe [3]

To cite: DiNicolantonio JJ, McCarty MF, O'Keefe JH. Coenzyme Q10 deficiency can be expected to compromise Sirt1 activity. *Open Heart* 2022;**9**:e001927. doi:10.1136/openhrt-2021-001927

Received 1 December 2021
Accepted 28 February 2022

[1]Department of Preventive Cardiology, Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA
[2]Catalytic Longevity, Encinitas, California, USA
[3]Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, Missouri, USA

Correspondence to
Dr James J DiNicolantonio; jjdinicol@gmail.com

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]

Contributors All authors contributed to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JJD is director of Scientific Affairs at Advanced Ingredients for Dietary Products (AIDP) and is affiliated with companies that sell CoQ10. MM and JO own supplement companies.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs

James J DiNicolantonio http://orcid.org/0000-0002-7888-1528

James H O'Keefe http://orcid.org/0000-0002-3376-5822

REFERENCES

1 Awad AM, Bradley MC, Fernández-Del-Río L, *et al*. Coenzyme Q_{10} deficiencies: pathways in yeast and humans. *Essays Biochem* 2018;62:361–76.
2 Alcázar-Fabra M, Trevisson E, Brea-Calvo G. Clinical syndromes associated with Coenzyme Q_{10} deficiency. *Essays Biochem* 2018;62:377–98.
3 Hargreaves I, Heaton RA, Mantle D. Disorders of human coenzyme Q10 metabolism: an overview. *Int J Mol Sci* 2020;21:6695.
4 Aaseth J, Alexander J, Alehagen U. Coenzyme Q10 supplementation – in ageing and disease. *Mech Ageing Dev* 2021;197:111521.
5 Fazakerley DJ, Chaudhuri R, Yang P, *et al*. Mitochondrial CoQ deficiency is a common driver of mitochondrial oxidants and insulin resistance. *Elife* 2018;7. doi:10.7554/eLife.32111. [Epub ahead of print: 06 02 2018].
6 Braidy N, Guillemin GJ, Mansour H, *et al*. Age related changes in NAD+ metabolism oxidative stress and SIRT1 activity in Wistar rats. *PLoS One* 2011;6:e19194.
7 Shin SY, Kim TH, Wu H, *et al*. Sirt1 activation by methylene blue, a repurposed drug, leads to AMPK-mediated inhibition of steatosis and steatohepatitis. *Eur J Pharmacol* 2014;727:115–24.
8 Tobiume K, Matsuzawa A, Takahashi T, *et al*. Ask1 is required for sustained activations of JNK/p38 MAP kinases and apoptosis. *EMBO Rep* 2001;2:222–8.
9 Matsuzawa A, Nishitoh H, Tobiume K, *et al*. Physiological roles of ASK1-mediated signal transduction in oxidative stress- and endoplasmic reticulum stress-induced apoptosis: advanced findings from ASK1 knockout mice. *Antioxid Redox Signal* 2002;4:415–25.
10 Matsukawa J, Matsuzawa A, Takeda K, *et al*. The ASK1-MAP kinase cascades in mammalian stress response. *J Biochem* 2004;136:261–5.
11 Gao Z, Zhang J, Kheterpal I, *et al*. Sirtuin 1 (SIRT1) protein degradation in response to persistent c-Jun N-terminal kinase 1 (JNK1) activation contributes to hepatic steatosis in obesity. *J Biol Chem* 2011;286:22227–34.
12 Lin Z, Yang H, Kong Q, *et al*. USP22 antagonizes p53 transcriptional activation by deubiquitinating SIRT1 to suppress cell apoptosis and is required for mouse embryonic development. *Mol Cell* 2012;46:484–94.
13 Ao N, Liu Y, Feng H, *et al*. Ubiquitin-specific peptidase USP22 negatively regulates the STAT signaling pathway by deubiquitinating SIRT1. *Cell Physiol Biochem* 2014;33:1863–75.
14 Kim TH, Yang YM, Han CY, *et al*. Gα12 ablation exacerbates liver steatosis and obesity by suppressing USP22/SIRT1-regulated mitochondrial respiration. *J Clin Invest* 2018;128:5587–602.
15 Xiong J, Che X, Li X, *et al*. Cloning and characterization of the human USP22 gene promoter. *PLoS One* 2012;7:e52716.
16 Xiong J, Gong Z, Zhou X, *et al*. p38 mitogen-activated protein kinase inhibits *USP22* transcription in HeLa cells. *Biomed Rep* 2015;3:461–7.
17 D'Addario M, Arora PD, McCulloch CA. Role of p38 in stress activation of Sp1. *Gene* 2006;379:51–61.
18 Lombard DB, Zwaans BMM. Sirt3: as simple as it seems? *Gerontology* 2014;60:56–64.
19 Chen J-X, Yang L, Sun L, *et al*. Sirtuin 3 ameliorates lung senescence and improves type II alveolar epithelial cell function by enhancing the FoxO3a-Dependent antioxidant defense mechanism. *Stem Cells Dev* 2021;30:843–55.
20 Chen Y, Zhang J, Lin Y, *et al*. Tumour suppressor SIRT3 deacetylates and activates manganese superoxide dismutase to scavenge ROS. *EMBO Rep* 2011;12:534–41.
21 Zhang X, Ren X, Zhang Q, *et al*. PGC-1α/ERRα-Sirt3 pathway regulates DAergic neuronal death by directly deacetylating SOD2 and ATP synthase β. *Antioxid Redox Signal* 2016;24:312–28.
22 Giralt A, Hondares E, Villena JA, *et al*. Peroxisome proliferator-activated receptor-gamma coactivator-1alpha controls transcription of the SIRT3 gene, an essential component of the thermogenic brown adipocyte phenotype. *J Biol Chem* 2011;286:16958–66.
23 Fernandez-Marcos PJ, Auwerx J. Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. *Am J Clin Nutr* 2011;93:884S–90.
24 Cantó C, Gerhart-Hines Z, Feige JN, *et al*. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. *Nature* 2009;458:1056–60.
25 Samimi F, Baazm M, Eftekhar E, *et al*. Possible antioxidant mechanism of coenzyme Q10 in diabetes: impact on Sirt1/Nrf2 signaling pathways. *Res Pharm Sci* 2019;14:524–33.

26 Chen B, Wu L, Cao T, *et al*. MiR-221/SIRT1/Nrf2 signal axis regulates high glucose induced apoptosis in human retinal microvascular endothelial cells. *BMC Ophthalmol* 2020;20:300.
27 Yousefi Z, Nourbakhsh M, Abdolvahabi Z, *et al*. microRNA-141 is associated with hepatic steatosis by downregulating the sirtuin1/AMP-activated protein kinase pathway in hepatocytes. *J Cell Physiol* 2020;235:880–90.
28 Liu H-N, Cao N-J, Li X, *et al*. Serum microRNA-211 as a biomarker for diabetic retinopathy via modulating sirtuin 1. *Biochem Biophys Res Commun* 2018;505:1236–43.
29 Xue M, Li Y, Hu F, *et al*. High glucose up-regulates microRNA-34a-5p to aggravate fibrosis by targeting SIRT1 in HK-2 cells. *Biochem Biophys Res Commun* 2018;498:38–44.
30 Yuan Y, Cruzat VF, Newsholme P, *et al*. Regulation of SIRT1 in aging: roles in mitochondrial function and biogenesis. *Mech Ageing Dev* 2016;155:10–21.
31 Das S, Mitrovsky G, Vasanthi HR, *et al*. Antiaging properties of a grape-derived antioxidant are regulated by mitochondrial balance of fusion and fission leading to mitophagy triggered by a signaling network of Sirt1-Sirt3-Foxo3-PINK1-PARKIN. *Oxid Med Cell Longev* 2014;2014:1–13.
32 Gupta P, Sharma G, Lahiri A, *et al*. FOXO3a acetylation regulates PINK1, mitophagy, inflammasome activation in murine palmitate-conditioned and diabetic macrophages. *J Leukoc Biol* 2022;111:611–27. doi:10.1002/JLB.3A0620-348RR
33 Cotán D, Cordero MD, Garrido-Maraver J, *et al*. Secondary coenzyme Q10 deficiency triggers mitochondria degradation by mitophagy in MELAS fibroblasts. *Faseb J* 2011;25:2669–87.
34 Rodríguez-Hernández A, Cordero MD, Salviati L, *et al*. Coenzyme Q deficiency triggers mitochondria degradation by mitophagy. *Autophagy* 2009;5:19–32.
35 Zhang P, Chen S, Tang H, *et al*. CoQ10 protects against acetaminophen-induced liver injury by enhancing mitophagy. *Toxicol Appl Pharmacol* 2021;410:115355.
36 Sun J, Zhu H, Wang X, *et al*. CoQ10 ameliorates mitochondrial dysfunction in diabetic nephropathy through mitophagy. *J Endocrinol* 201910.1530/JOE-18-0578. [Epub ahead of print: 01 Jan 2019].
37 Yeung F, Hoberg JE, Ramsey CS, *et al*. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *Embo J* 2004;23:2369–80.
38 Salminen A, Kauppinen A, Suuronen T, *et al*. SIRT1 longevity factor suppresses NF-kappaB -driven immune responses: regulation of aging via NF-kappaB acetylation? *Bioessays* 2008;30:939–42.
39 Surh Y-J, Kundu JK, Na H-K, . Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals. *Planta Med* 2008;74:1526–39.
40 Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J* 1984;108:188–93.
41 Russell RC, Yuan H-X, Guan K-L. Autophagy regulation by nutrient signaling. *Cell Res* 2014;24:42–57.
42 Zhao M, Klionsky DJ. Ampk-Dependent phosphorylation of ULK1 induces autophagy. *Cell Metab* 2011;13:119–20.
43 Kim J, Guan K-L. Regulation of the autophagy initiating kinase ULK1 by nutrients: roles of mTORC1 and AMPK. *Cell Cycle* 2011;10:1337–8.
44 Park H, Kaushik VK, Constant S, *et al*. Coordinate regulation of malonyl-CoA decarboxylase, sn-glycerol-3-phosphate acyltransferase, and acetyl-CoA carboxylase by AMP-activated protein kinase in rat tissues in response to exercise. *J Biol Chem* 2002;277:32571–7.
45 Gracia-Sancho J, Villarreal G, Zhang Y, *et al*. Activation of SIRT1 by resveratrol induces KLF2 expression conferring an endothelial vasoprotective phenotype. *Cardiovasc Res* 2010;85:514–9.
46 Cui X, Liu X, Feng H, *et al*. Grape seed proanthocyanidin extracts enhance endothelial nitric oxide synthase expression through 5'-AMP activated protein kinase/Surtuin 1-Krüpple like factor 2 pathway and modulate blood pressure in ouabain induced hypertensive rats. *Biol Pharm Bull* 2012;35:2192–7.
47 Boon RA, Horrevoets AJG. Key transcriptional regulators of the vasoprotective effects of shear stress. *Hamostaseologie* 2009;29:39–43.
48 Turpaev KT. Transcription factor KLF2 and its role in the regulation of inflammatory processes. *Biochemistry* 2020;85:54–67.
49 Mattagajasingh I, Kim C-S, Naqvi A, *et al*. SIRT1 promotes endothelium-dependent vascular relaxation by activating endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A* 2007;104:14855–60.
50 Vaziri H, Dessain SK, Ng Eaton E, *et al*. hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. *Cell* 2001;107:149–59.
51 Lee S-H, Lee J-H, Lee H-Y, *et al*. Sirtuin signaling in cellular senescence and aging. *BMB Rep* 2019;52:24–34.
52 Lagunas-Rangel FA. Current role of mammalian sirtuins in DNA repair. *DNA Repair* 2019;80:85–92.
53 Giannakou ME, Partridge L. The interaction between FOXO and SIRT1: tipping the balance towards survival. *Trends Cell Biol* 2004;14:408–12.
54 Zhao X, Liu Y, Zhu G, *et al*. SIRT1 downregulation mediated manganese-induced neuronal apoptosis through activation of FOXO3a-Bim/PUMA axis. *Sci Total Environ* 2019;646:1047–55.
55 Ponugoti B, Kim D-H, Xiao Z, *et al*. Sirt1 deacetylates and inhibits SREBP-1c activity in regulation of hepatic lipid metabolism. *J Biol Chem* 2010;285:33959–70.
56 Qiao L, Shao J. Sirt1 regulates adiponectin gene expression through Foxo1-C/enhancer-binding protein alpha transcriptional complex. *J Biol Chem* 2006;281:39915–24.
57 Wang A, Li T, An P, *et al*. Exendin-4 upregulates adiponectin level in adipocytes via Sirt1/Foxo-1 signaling pathway. *PLoS One* 2017;12:e0169469.
58 Costa CdosS, Rohden F, Hammes TO, *et al*. Resveratrol upregulated SIRT1, FOXO1, and adiponectin and downregulated PPARγ1-3 mRNA expression in human visceral adipocytes. *Obes Surg* 2011;21:356–61.
59 Mortensen SA, Rosenfeldt F, Kumar A, *et al*. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail* 2014;2:641–9.
60 Lei L, Liu Y. Efficacy of coenzyme Q10 in patients with cardiac failure: a meta-analysis of clinical trials. *BMC Cardiovasc Disord* 2017;17:196.
61 Ho MJ, Bellusci A, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. *Cochrane Database Syst Rev* 2009:CD007435. doi:10.1002/14651858.CD007435.pub2
62 Tabrizi R, Akbari M, Sharifi N, *et al*. The effects of coenzyme Q10 supplementation on blood pressures among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. *High Blood Press Cardiovasc Prev* 2018;25:41–50.
63 Raut CP, Sethi KS, Kohale B, *et al*. Subgingivally delivered coenzyme Q10 in the treatment of chronic periodontitis among smokers: a randomized, controlled clinical study. *J Oral Biol Craniofac Res* 2019;9:204–8.
64 Manthena S, Rao MVR, Penubolu LP, *et al*. Effectiveness of COQ10 oral supplements as an adjunct to scaling and root planing in improving periodontal health. *J Clin Diagn Res* 2015;9:ZC26-8.
65 Lin B, Zhao H, Li L, *et al*. Sirt1 improves heart failure through modulating the NF-κB p65/microRNA-155/BNDF signaling cascade. *Aging* 2020;13:14482–98.
66 Mu W, Zhang Q, Tang X, *et al*. Overexpression of a dominant-negative mutant of SIRT1 in mouse heart causes cardiomyocyte apoptosis and early-onset heart failure. *Sci China Life Sci* 2014;57:915–24.
67 Gu XS, Wang ZB, Ye Z, *et al*. Resveratrol, an activator of SIRT1, upregulates AMPK and improves cardiac function in heart failure. *Genet Mol Res* 2014;13:323–35.
68 Tanno M, Kuno A, Horio Y, *et al*. Emerging beneficial roles of sirtuins in heart failure. *Basic Res Cardiol* 2012;107:273.
69 Bhatt SR, Lokhandwala MF, Banday AA. Resveratrol prevents endothelial nitric oxide synthase uncoupling and attenuates development of hypertension in spontaneously hypertensive rats. *Eur J Pharmacol* 2011;667:258–64.
70 Dolinsky VW, Chakrabarti S, Pereira TJ, *et al*. Resveratrol prevents hypertension and cardiac hypertrophy in hypertensive rats and mice. *Biochim Biophys Acta* 2013;1832:1723–33.
71 Li X, Dai Y, Yan S, *et al*. Resveratrol lowers blood pressure in spontaneously hypertensive rats via calcium-dependent endothelial NO production. *Clin Exp Hypertens* 2016;38:287–93.
72 Kim Y-H, Hwang JH, Kim K-S, *et al*. NAD(P)H:quinone oxidoreductase 1 activation reduces blood pressure through regulation of endothelial nitric oxide synthase acetylation in spontaneously hypertensive rats. *Am J Hypertens* 2015;28:50–7.
73 Andrade EF, Orlando DR, Araújo Amanda Melo Sant'Anna, *et al*. Can resveratrol treatment control the progression of induced periodontal disease? A systematic review and meta-analysis of preclinical studies. *Nutrients* 2019;11. doi:10.3390/nu11050953. [Epub ahead of print: 26 Apr 2019].
74 Farhangi MA, Alipour B, Jafarvand E, *et al*. Oral coenzyme Q10 supplementation in patients with nonalcoholic fatty liver disease: effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress. *Arch Med Res* 2014;45:589–95.

75 Farsi F, Mohammadshahi M, Alavinejad P, *et al*. Functions of coenzyme Q10 supplementation on liver enzymes, markers of systemic inflammation, and adipokines in patients affected by nonalcoholic fatty liver disease: a double-blind, placebo-controlled, randomized clinical trial. *J Am Coll Nutr* 2016;35:346–53.
76 Botham KM, Napolitano M, Bravo E. The emerging role of disturbed CoQ metabolism in nonalcoholic fatty liver disease development and progression. *Nutrients* 2015;7:9834–46.
77 Chen K, Chen X, Xue H, *et al*. Coenzyme Q10 attenuates high-fat diet-induced non-alcoholic fatty liver disease through activation of the AMPK pathway. *Food Funct* 2019;10:814–23.
78 Dludla PV, Orlando P, Silvestri S, *et al*. Coenzyme Q10 supplementation improves adipokine levels and alleviates inflammation and lipid peroxidation in conditions of metabolic syndrome: a meta-analysis of randomized controlled trials. *Int J Mol Sci* 2020;21:3247.
79 Hui X, Zhang M, Gu P, *et al*. Adipocyte SIRT1 controls systemic insulin sensitivity by modulating macrophages in adipose tissue. *EMBO Rep* 2017;18:645–57.
80 Quiles JL, Barriocanal-Casado E. The Paradox of Coenzyme Q(10) in Aging. *Nutrients* 2019;11:2221.
81 Beyer RE, Burnett BA, Cartwright KJ, *et al*. Tissue coenzyme Q (ubiquinone) and protein concentrations over the life span of the laboratory rat. *Mech Ageing Dev* 1985;32:267–81.
82 Kalén A, Appelkvist EL, Dallner G. Age-Related changes in the lipid compositions of rat and human tissues. *Lipids* 1989;24:579–84.
83 Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc Natl Acad Sci U S A* 1985;82:901–4.
84 Kennedy C, Köller Y, Surkova E. Effect of coenzyme Q10 on statin-associated myalgia and adherence to statin therapy: a systematic review and meta-analysis. *Atherosclerosis* 2020;299:1–8.
85 Sztretye M, Dienes B, Gönczi M, *et al*. Astaxanthin: a potential mitochondrial-targeted antioxidant treatment in diseases and with aging. *Oxid Med Cell Longev* 2019;2019:1–14.
86 Jia Y, Kim J-Y, Jun H-J, *et al*. The natural carotenoid astaxanthin, a PPAR-α agonist and PPAR-γ antagonist, reduces hepatic lipid accumulation by rewiring the transcriptome in lipid-loaded hepatocytes. *Mol Nutr Food Res* 2012;56:878–88.
87 Jia Y, Wu C, Kim J, *et al*. Astaxanthin reduces hepatic lipid accumulations in high-fat-fed C57BL/6J mice via activation of peroxisome proliferator-activated receptor (PPAR) alpha and inhibition of PPAR gamma and Akt. *J Nutr Biochem* 2016;28:9–18.
88 Choi C-I. Astaxanthin as a peroxisome proliferator-activated receptor (PPAR) modulator: its therapeutic implications. *Mar Drugs* 2019;17. doi:10.3390/md17040242. [Epub ahead of print: 23 Apr 2019].
89 Duncan JG, Fong JL, Medeiros DM, *et al*. Insulin-resistant heart exhibits a mitochondrial biogenic response driven by the peroxisome proliferator-activated receptor-alpha/PGC-1alpha gene regulatory pathway. *Circulation* 2007;115:909–17.
90 Kersten S. Integrated physiology and systems biology of PPARα. *Mol Metab* 2014;3:354–71.
91 Aaseth J, Alexander J, Alehagen U. Coenzyme Q_{10} supplementation - In ageing and disease. *Mech Ageing Dev* 2021;197:111521.
92 Qu H, Meng Y-Y, Chai H, *et al*. The effect of statin treatment on circulating coenzyme Q10 concentrations: an updated meta-analysis of randomized controlled trials. *Eur J Med Res* 2018;23:57.
93 McCarty MF, DiNicolantonio JJ, Iloki-Assanga S, *et al*. Ferulic acid and berberine, via SIRT1 and AMPK, may act as cell cleansing promoters of healthy longevity. *Open Heart*. In Press 2021.
94 Du K, Fang X, Li Z. Ferulic acid suppresses interleukin-1β-induced degeneration of chondrocytes isolated from patients with osteoarthritis through the SIRT1/AMPK/PGC-1α signaling pathway. *Immun Inflamm Dis* 2021;9:710–20.
95 Xu T, Song Q, Zhou L, *et al*. Ferulic acid alleviates lipotoxicity-induced hepatocellular death through the SIRT1-regulated autophagy pathway and independently of AMPK and Akt in AML-12 hepatocytes. *Nutr Metab* 2021;18:13.
96 Yang Y, Jiang S, Dong Y, *et al*. Melatonin prevents cell death and mitochondrial dysfunction via a SIRT1-dependent mechanism during ischemic-stroke in mice. *J Pineal Res* 2015;58:61–70.
97 Hong S, Moreno-Navarrete JM, Wei X, *et al*. Nicotinamide N-methyltransferase regulates hepatic nutrient metabolism through SIRT1 protein stabilization. *Nat Med* 2015;21:887–94.
98 Ghosh N, Das A, Biswas N, *et al*. Urolithin A augments angiogenic pathways in skeletal muscle by bolstering NAD^+ and SIRT1. *Sci Rep* 2020;10:20184.
99 Gomes AP, Duarte FV, Nunes P, *et al*. Berberine protects against high fat diet-induced dysfunction in muscle mitochondria by inducing SIRT1-dependent mitochondrial biogenesis. *Biochim Biophys Acta* 2012;1822:185–95.
100 Cantó C, Houtkooper RH, Pirinen E, *et al*. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab* 2012;15:838–47.
101 Lillioja S, Neal AL, Tapsell L, *et al*. Whole grains, type 2 diabetes, coronary heart disease, and hypertension: links to the aleurone preferred over indigestible fiber. *BioFactors* 2013;39:242–58.
102 McCarty MF, Assanga SBI. Ferulic acid may target MyD88-mediated pro-inflammatory signaling - Implications for the health protection afforded by whole grains, anthocyanins, and coffee. *Med Hypotheses* 2018;118:114–20.
103 Hasheminezhad SH, Boozari M, Iranshahi M, *et al*. A mechanistic insight into the biological activities of urolithins as gut microbial metabolites of ellagitannins. *Phytother Res* 2022;36:112-146.