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Review Article
Skeletal Protective Effect of Coenzyme Q10: A Review

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Abstract

The imbalance between osteoclastic bone resorption and osteoblastic bone formation due to inflammation and oxidative stress contributes to bone loss and osteoporosis. In this regards, dietary antioxidative and anti-inflammatory compounds may delay the progression of osteoporosis. Coenzyme Q10 is an example of dietary compounds with both antioxidative and anti-inflammatory activities. Coenzyme Q10 can be synthesized endogenously or obtained from the diet. Experimental studies showed that Coenzyme Q10 could prevent bone loss in animal models of osteoporosis due to ovariectomy and high-fat diets. Evidence suggests that Coenzyme Q10 protects bone health by blocking RANKL-induced osteoclastogenesis and increasing osteogenic differentiation. Considering the other health effects of Coenzyme Q10 , it can be used to prevent multiple conditions among the middle-aged and elderly population. However, the skeletal protective effects of Coenzyme Q10 are yet to be validated in clinical trials. This study gap needs to be bridged for further development of Coenzyme Q10 as supplements for skeletal health.

Key words: Anti-inflammatory, antioxidant, bone, osteoblast, osteoclast, osteoporosis, ubiquinone

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Osteoporosis is a bone disease characterized by deterioration of skeletal mass and micro-architecture, which leads to impaired skeletal strength resulting in bone fragility and increased susceptibility to fracture[1]. An estimate in 2010 reported that 21 million men and 137 million women globally had a high probability of osteoporotic fracture and 55% of them were from Asia[2]. An updated hip fracture projection in Asia revealed that Malaysia will experience a 3.55-fold increase in hip fracture incidence[3] by 2050 compared to 2018. Osteoporotic fractures are rampant in women after 55 years and in men after 65 years, thereby giving rise to bone-associated morbidities, increased mortality and health-care costs which are burdensome to individuals, families and the society[4].

Many therapeutic agents for osteoporosis are available to patients with a high risk of osteoporosis (low bone mineral (BMD) and/or clinical risk factors of osteoporosis) or fragility fractures[5]. The foremost treatment for most osteoporotic patients is antiresorptive drugs, which suppress the formation and function of osteoclasts responsible for bone resorption. These drugs include bisphosphonates, denosumab and selective oestrogen receptor modulators. Hormonal therapy is prescribed to women up to 10 years after menopause[6]. Teriparatide is the only clinically approved anabolic agent that increases new bone formation by osteoblasts[5]. Lifestyle intervention is an essential part of osteoporosis prevention. Weight-bearing exercises are important in strengthening bone density and preventing falls[7]. A combination of adequate calories, protein, calcium and vitamin D is vital in maintaining bone health[8].

Bone loss occurs when the rate of osteoclastic bone resorption overwhelms osteoblastic bone formation[9]. Inflammation is implicated in this skewed bone remodelling and the subsequent development of osteoporosis[10]. Inflammation promotes bone resorption by upregulating the expression of receptor activator of nuclear factor-B (RANK) and its functional ligand (RANKL) as well as macrophage colony-stimulating factor (M-CSF), which subsequently enhances formation and function of osteoclasts[9]. Besides, oxidative stress is also linked to the pathogenesis of osteoporosis through changes in reactive oxygen species (ROS) and/or antioxidant systems. ROS impair the formation of osteoblasts, stimulate the apoptosis of osteoblasts and osteocytes and promote the formation of osteoclasts. This will lead to bone loss and osteoporosis[11]. Incorporation of antioxidative and anti-inflammatory compounds in the diet may delay the progression of osteoporosis[11].

Coenzyme Q10 (CoQ10) is an example of natural compounds with both antioxidant and anti-inflammatory properties. The CoQ10 or ubiquinone is a lipophilic vitamin-like molecule involved in the production and control of cellular bioenergy, pyrimidine synthesis, physicochemical properties of cellular membranes and gene expression[12]. The CoQ10 is predominantly found in organs of animals, such as kidney, liver and heart, as well as in meats and fish, such as beef, sardines and mackerel. CoQ10 can also be detected in soy oil and peanuts[13].

The CoQ10 also possesses anti-inflammatory and antioxidant properties. Meta-analyses of clinical studies have proven that supplementation with CoQ10 substantially decreases the level of inflammatory mediators, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) respectively[14,15]. This is achieved by the suppression of nuclear factor kappa-light-chain-enhancer of activated B cell (NFκB), which is the main regulator of inflammation[16]. Modulation of NFκB and factor erythroid 2-related factor 2 pathways by CoQ10 contributes to its antioxidant properties and prevent oxidative damage to the cells[17]. Endogenous synthesis of CoQ10 can meet the body daily requirement but the production reduces significantly with age[18,19]. The impaired production of CoQ10 due to age may underly the pathogenesis of many oxidative stress-related metabolic conditions including osteoporosis[20-23].

Previous studies reported that CoQ10 could regulate osteoblast and osteoclast differentiation[24]. Supplementation with CoQ10 reduced RANKL-induced osteoclastogenesis, inflammatory mediators and oxidant factors in zymosan-induced arthritis[25]. It also suppressed ROS-induced IkBa signalling pathways and prevented osteoclastogenesis in bone marrow-derived monocytes (BMM) and RAW 264.7 cell lines[24]. Another study reported that TNF-α was reduced in spinal cord injury (SCI) following CoQ10 supplementation[26]. The review aimed to provide an overview of the skeletal protective effects of CoQ10 and its potential role in the prevention of osteoporosis.

Role of CoQ10 in protecting bone health: As illustrated previously, osteoporosis occurs due to an imbalance in bone remodelling, skewing towards bone resorption by osteoclasts. Improving bone formation could be a strategy to prevent bone loss. Bone marrow stromal cells (BMSCs) cultured with CoQ10 showed increased expression of osteogenic markers, such as runt-related transcription factor 2 (RUNX-2), osteocalcin (OCN) and alkaline phosphatase (ALP), which suggests that CoQ10 promotes osteogenic differentiation of BMSCs[27]. Several studies showed that CoQ10 increased

osteoblastogenesis and reduced osteoclastogenesis concurrently[24,27-31]. In the studies by Moon *et al.*[24,31], BMM and RAW 264.7 cultured with CoQ10 showed reduced osteoclast cell differentiation as evidenced by a reduction in gene expression of osteoclast differentiation markers, such as nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1), tartrate-resistant acid phosphatase (TRAP) and osteoclast-associated immunoglobulin-like receptor (OSCAR). The combined effects of increased bone formation and reduced bone resorption could lead to improved bone health.

Animal experiments support the role of CoQ10 in the prevention and treatment of osteoporosis and other inflammatory bone diseases. A study by Zheng *et al.*[27] showed that CoQ10 supplementation (1 mg kg^{-1} i.p. every 5 days for 3 months) increased serum calcium and osteoprotegerin (OPG) and reduced serum parathyroid hormone in ovariectomy-induced osteoporosis. They also reported an increase in femoral BMD, trabecular number (Tb. N), bone volume fraction (BV/TV) and trabecular thickness (Tb. Th) and a decrease in trabecular separation (Tb. Sp) in the CoQ10 supplemented ovariectomized rats. The CoQ10 was also reported to increase BMD and bone mineral content (BMC) by reducing osteoclastogenesis and increasing osteoblastogenesis as evidenced by gene expression of relevant markers in SCI-induced osteoporosis model. This effect was shown to be mediated by a decrease in inflammation and oxidative stress in bone[26,30].

High-fat diets have been linked to lower BMD, as well as microstructural and biomechanical deterioration of bone, subsequently leading to osteoporosis[32-34]. Several studies by Zheng *et al.*[27] and Varela-Lopez *et al.*[28,35] reported that CoQ10 supplementation (50 mg kg^{-1} and 2.5 mg kg^{-1}, respectively) for 24 months increased BMD and BMC and reduced age-related alveolar bone loss associated with monounsaturated fatty acids or n-6 polyunsaturated fatty acid-rich diets. CoQ10 did this by increasing the OPG levels, which can hinder RANK-RANKL binding and osteoclast formation.

The skeletal effects of CoQ10 extend beyond osteoporosis. The CoQ10 (20 mg kg^{-1} for 7 weeks) decreased RANKL-induced osteoclastogenesis associated with zymosan-induced arthritis (ZIA) in mice[25]. In another study, CoQ10 (10 mg kg^{-1} for 4 weeks) also increased osteocyte count and decreased osteonecrosis associated with corticosteroid-induced osteonecrosis inrats[36]. This could be attributed to the anabolic effects of CoQ10.

The anti-inflammatory activities of CoQ10 supplementation could prevent back pain. A study by Wang *et al.*[37] reported that CoQ10 suppressed cyclooxygenase-2, IL-6, TNF-α and inducible nitrate oxide synthase levels in intervertebral discs tissue induced by IL-1β. They also reported that the production of cartilage-anabolic biomarkers, such as collagen 2, aggrecan and Sox-9 in human nucleus pulposus cells cultured with CoQ10. These observations showed that Co-Q10 supplementation could reduce inflammation and degeneration of the intervertebral disc, which could lead to back pain.

There is a lack of human studies on the relationship between CoQ10 and skeletal health, either from cross-sectional or prospective cohort studies. Similarly, there is no clinical trial conducted to study the effects of CoQ10 supplementation on skeletal health in humans. A meta-analysis of clinical trials showed that CoQ10 supplementation was associated with a substantial reduction in TNF-α plasma levels in patients with various metabolic conditions[15]. Low-grade chronic inflammation caused by metabolic syndrome is suggested to induce bone loss and osteoporosis[38]. It should be noted that eight of the nine studies included in this meta-analysis were from Asia[15], thus hindering the generalization of this observation to other populations. In another double-blind randomized clinical control trial by Abdollahzad *et al.*[39], 22 rheumatoid arthritis patients receiving CoQ10 (100 mg/day) for 2 months showed decreased malondialdehyde level (a marker of lipid peroxidation) and TNF-α compared to placebo at the end of the study. However, changes to the enzymatic and non-enzymatic antioxidant system in the body were not studied in this trial. A summary of the skeletal effects of CoQ10 is presented in Table 1 and Fig. 1.

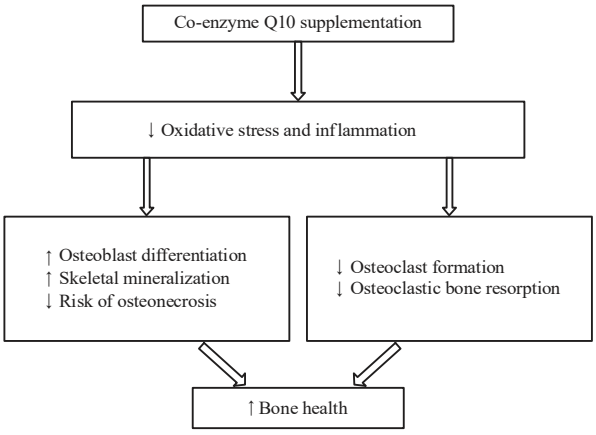

Fig. 1: Bone protective mechanism of Coenzyme Q10[15,24-28,30-39]

Table 1: Evidence of CoQ10 in protecting skeletal health

Animal studies

Study design	Findings	Notes	References
Animals: 30 adult female Wistar rats (200-250 g) Mode of bone loss: Ovariectomy and spinal cord injury (SCI) (OVX-SCI) Treatment: 10 mg kg^{-1} of CoQ10 in 0.4 mL of sesame oil daily for 3 weeks Control: • Negative: OVX-SCI+no treatment and OVX-SCI+sesame oil • Positive: No	↓ Tumour necrosis factor-α (TNF-α) compared to the untreated OVX-SCI group ↓ Demyelination at compression site compared to untreated OVX-SCI group	Strengths: • Adequate comparison between treated and untreated groups • Sufficient number of animals Limitations: • No positive control • No measurement of bone parameters	Hassanzadeh *et al.*[26]
Animals: 40 female Sprague Dawley rats (8 months old) Mode of bone loss: Ovariectomy (OVX) Treatment: 1, 10 and 20 mg kg^{-1} of CoQ10 every 5 days for 3 months Control: • Negative: OVX+no treatment • Positive: No	↑ Serum calcium/OPG, BV/TV/Tb.Th and serum PTH at 20 mg kg^{-1} compared to untreated OVX group ↑ BMD/Tb.N ↓ Tb.Sp at 1, 10 or 20 mg kg^{-1} compared to untreated OVX group	Strengths: • Adequate comparison between treated and untreated groups • Adequate treatment period • Sufficient number of animals • Bone parameters measured Limitations: • No positive control	Zheng *et al.*[27]
Animals: 48 male Wistar rats (80-90 g) Mode of bone loss: Age+virgin olive oil (V group) and age+sunflower oil (S group) Treatment: 2.5 mg kg^{-1} of CoQ10 daily for 24 months Control: • Negative: Age+virgin olive oil (V group) and age+sunflower oil (S group) • Positive: No	↑ BMD and BMC compared to V and S group at 24 months only ↓ OPG levels compared to S group	Strengths: • Adequate treatment period • Sufficient number of animals Limitations: • No positive control	Varela-Lopez *et al.*[28]
Animals: 24 male Wistar rats (80-90 g) Mode of bone loss: Age+fish oil-based diet Treatment: 2.5mg kg^{-1} of CoQ10 daily for 24 months Control: Negative: Age+fish oil-based diet Positive: No	↑ Plasma CoQ10 and BMD compared to negative control group ↓ RANKL, RANKL/OPG ↑ OPG at 24 months compared to negative control group	Strengths: • Adequate treatment period • Sufficient number of animals Limitations: • No positive control	Varela-Lopez *et al.*[29]
Animals: 72 male Wistar rats (80-90 g) Mode of bone loss: Age+virgin olive oil (V group), age+sunflower oil (S group) and age+fish oil (F) Treatment: 50 mg kg^{-1} CoQ10 daily for 24 months Control: • Negative: No • Positive: No	↓ Alveolar bone loss	Strengths • Adequate treatment period • Sufficient number of animals Limitations: • No negative control • No positive control	Varela-Lopez *et al.*[35]
Animals: 20 SKG mice (7 weeks old) Mode of bone loss: Zymosan-induced arthritis (ZIA) Treatment: 20 mg kg^{-1} daily for 7 weeks Controls: • Negative: ZIA+20 mg kg^{-1} cotton seed oil • Positive: No	↓ Severity of arthritis and proinflammatory cytokines such as IL-21, IL-1β, IL-17, TNF-α and VEGF compared to negative control ↓ Bone erosion and cartilage damage compared to negative control ↓ TRAP positive cells in joint tissue and RANKL-induced osteoblastogenesis compared to negative control	Strengths: • The severity of arthritis well analysed • Adequate treatment period • Sufficient number of animals Limitations: • No positive control	Jhun *et al.*[25]

Table 1: Continue

Animal studies			
Study design	Findings	Notes	References
Animals: 40 Sprague-Dawley rats (8 weeks old, 170-200 g) Mode of bone loss: Spinal cord injury-induced osteoporosis (SCI) Treatment: 10 mg kg^{-1} of CoQ10 daily for 10 days Control: • Negative: SCI+no treatment • Positive: No	↓ Inflammatory markers (IL-6 and TNF-α) compared to the untreated SCI group ↓ BMD, BMC and Osteoblast specific gene (cbfa1) compared to the untreated SCI group ↓ Oxidative stress in bone ↓ Osteoclast specific genes(RANKL and cathepsin K) compared to the untreated SCI group	Strengths • Adequate treatment period • Sufficient number of animals Limitations: • No positive control	Zhang *et al.*[30]
Animals: 20 male Sprague-Dawley rats (250-300 g) Mode of bone loss: Corticosteroid-induced osteonecrosis model (COM) Treatment: 10 mg kg^{-1} of CoQ10 in soybean oil once in 5 days for 4 weeks Control: • Negative: COM+soybean oil • Positive: No	↓ Oxidative stress and incidence osteonecrosis compared to negative control ↑ Osteocyte count compared to negative control	Strengths • Sufficient number of animals Limitation • Short duration of steroid treatment to confirm diagnosis of osteonecrosis • There was no testing to show that the animals developed osteonecrosis before the intervention treatment began • Treatment period was short (4 weeks) so results didn't show all stages of necrosis only the early stage • No positive control	Komurcu *et al.*[36]
Cell studies			
Cell line: Intravertebral discs (IVD) tissue dissected from mice and human nucleus pulposus (NP) cells isolated from human IVD cells retrieved from 48 lumbar disc degenerative disease patients (23-45 years) Treatment: 20mM of CoQ10 for 7 days Controls: • Negative: 10 ng mL^{-1} of IL-1β+no treatment • Positive: No	↓ Destruction of IVD compared to negative control ↓ Release of IL-1β-induced IL-6 and TNF-α compared to negative control	Strengths: • Adequate molecular testing for inflammatory markers Limitations: • No positive control • No bone markers tested	Wang *et al.*[37]
Cell line: Bone marrow stromal cells (BMSC's) from 8 female Sprague Dawley rats (8 months old) Treatment: 10, 20 or 100 mM of CoQ10 dissolved in soyabean oil for 24 h Controls: • Negative: Soyabean oil • Positive: No	↑ BMSC viability at 10 mM compared to negative control ↑ Expression of osteogenic markers (RUNX-2, OCN and ALP) at 20 and 100 mM compared to negative control	Strengths: • Adequate molecular testing was carried out Limitations: • No positive control • No induction of bone loss	Zheng *et al.*[27]
Cell line: Bone marrow-derived monocytes (BMM), RAW 264.7 and MC3T3-E1 cells Treatments: 10-100mM of CoQ10 Controls: • Negative: 0 mM CoQ10 • Positive: No	↓ RANKL-induced TRAP-positive multinucleated cells (osteoclasts) in both BMMs and RAW 264.7 cells compared to negative control ↓ Genetic markers of osteoclast differentiation (NFATc1, TRAP and osteoclast-associated immunoglobulin-like receptor) and H_2O_2-induced IκBα, p38 signalling pathways for osteoclastogenesis compared to negative control ↑ Osteoblastogenic markers and promoted matrix mineralization	Strengths: • Adequate molecular testing was carried out Limitations: • No positive control	Moon *et al.*[24]

Possible molecular mechanism of CoQ 10 in preserving bone health: The CoQ10 is evidenced to modulate the formation of osteoblasts and osteoclasts as discussed above. These 2 cells are the major regulators of the skeletal remodeling process. The mechanism by which CoQ10 exerts these effects are reviewed in this section.

The NFκB pathway plays an important role in the inflammatory cascade and the formation of osteoclasts. The CoQ10 was shown to decrease the expression of p65, a marker of activated NFκB pathway in neurons in rats with type-2 diabetic mellitus. Furthermore, gene expression of other inflammatory components in the spinal cord of the rats, such as C-C motif chemokine ligand, C-X-C motif chemokine 10 and toll-like receptor (TLR) 4 was also reduced[40]. These observations are highly relevant to skeletal health as TLR signalling and NFκB are associated with osteoporosis[41]. In the study of Moon *et al.*[31], CoQ10 reduced NFATc1 expression in osteoclasts progenitors, which is a component downstream of NFkB in regulating osteoclastogenesis. In the subsequent study, Moon *et al.*[24] showed that CoQ10 blocked RANKL-induced osteoclastogenesis by suppressing activation of p38 (activator of NFκB pathway) and degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IKBα) (a suppressor of NFκB pathway) and phosphorylation of c-Jun N-terminal kinase (JNK).

Phosphatase and tensin homolog (PTEN)/ phosphoinositide 3-kinases (PI3K)/serine/threonine-protein kinases (AKT) is a pathway known to regulate osteoblast proliferation and differentiation. The PI3K mediates the pro-survival signals of various growth factors and antagonises the pro-apoptotic signals of Akt. Pten negatively regulates the PI3K pathway[42]. In the study of Zheng *et al.*[27], BMSCs of the rats treated with CoQ10 showed a reduction of Pten but an increment of p-P13K and p-AKT, subsequently promoting osteogenic differentiation of BMSCs.

The CoQ10 is also able to regulate the dynamic between osteoblasts and osteoclasts. The OPG and RANKL are two factors secreted by osteoblasts in regulating the formation of osteoclasts. The RANKL binds with RANK receptors on osteoclast progenitors to stimulate their differentiation. The OPG is a decoy receptor of RANKL that prevents the bindings of RANKL-RANK[43]. Two studies showed that CoQ10 can increase OPG level in animal models of osteoporosis but did not assess RANKL level[27,28]. Varela-Lopez *et al.*[29] showed that CoQ10 supplementation decrease RANKL/OPG ratio in rats fed with fish oil-based diet, thereby achieving its skeletal protective effects. These molecular actions of CoQ10 are summarized in Fig. 2.

Bioavailability and safety concerns of CoQ10 supplementation: The safety and efficacy of CoQ10 in treating human diseases have been examined in many studies[22]. Risk assessment of CoQ10 revealed that the observed safety levels (OSL) for CoQ10 was 1200 mg/day in humans[44,45], which is 20 mg kg^{-1} assuming the average weight of a human adult[46-49] is 60 kg. Deshmukh *et al.*[50] reported that

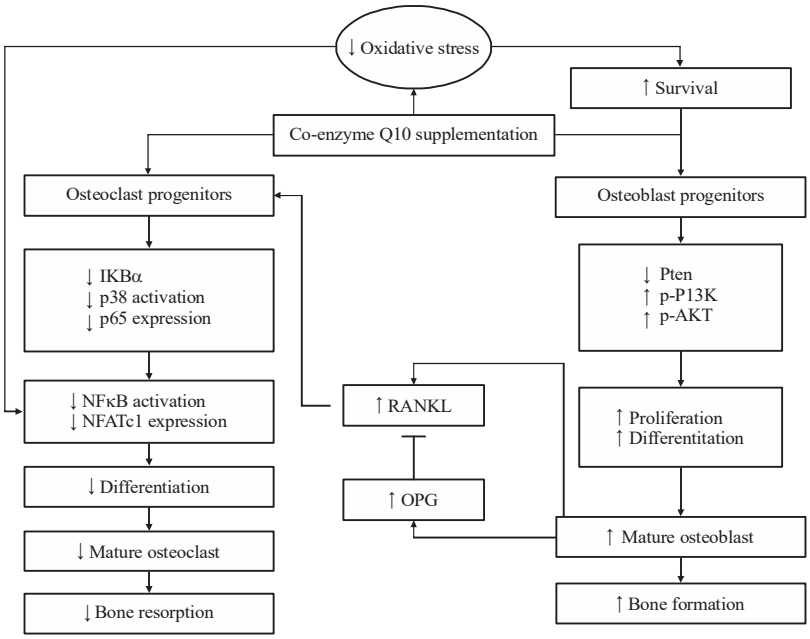

Fig. 2: Possible molecular mechanism of CoQ10 in preserving bone health[24,27-29,31,40-43]

Table 2: Animal doses used in study and their human equivalent doses (HED)

Animal doses used in studies (mg kg^{-1})	Animals	Human equivalent dose (mg kg^{-1})
1	Rat	0.162
2.5	Rat	0.405
10	Rat	1.62
20	Mouse	1.62
50	Rat	8.10

Animal doses are multiplied by 0.162 (for rats) and 0.081 (for mice) to get the HED, Human doses were converted from mg/day to mg kg^{-1} assuming the average weight for a human adult is 60 kg[46-49]

the no-observed-adverse-effect level (NOAEL) of CoQ10 administered orally to Sprague Dawley rats was 600 mg kg^{-1} body weight for males and 300 mg kg^{-1} body weight for females. All studies included in this review showed that the doses for animal studies (1-50 mg kg^{-1})[27,35] were not toxic as they were below the OLS and NOAEL reported. According to conversion shown in Table 2, animal dose of 10-50 mg kg^{-1} were translatable to reasonable human equivalent dose (HED).

Following oral administration of CoQ10, only a small fraction reaches the blood while the rest are eliminated through faeces[51]. The poor bioavailability of CoQ10 was due to its low aqueous solubility and high molecular weight[52,53]. The bioavailability of CoQ10 in humans also depends on the excipients of the formulation and the physiological characteristics of the recipients[54].

The use of CoQ10 in the treatment of several non-skeletal human pathologies has been studied. For examples, short-term daily treatment of 100 mg CoQ10 ($\leq$12 weeks) improved the left ventricular ejection fraction in patients suffering from heart failure[55]. In a 2 years randomized, controlled multicenter trial involving 420 patients with chronic heart failure, 300 mg/day of CoQ10 as adjunctive therapy reduced the occurrence of major cardiovascular events[56]. With regards to fertility, CoQ10 level in seminal fluid is considered an important biomarker of healthy sperm[57]. Supplementation of CoQ10 was reported to enhance semen parameters in men with idiopathic infertility[58]. Furthermore, CoQ10 (200-300 mg/day) enhanced sperm concentration, density, motility and morphology in men with infertility[59,60]. In a cancer study, female Sprague Dawley rats with 7,12-dimethyl benz(a)anthracene-induced mammary carcinoma showed increased expression of tumour suppressor gene manganese superoxide dismutase when treated with 40 mg kg^{-1} CoQ10 for 28 days[61]. Supplementation with CoQ10 (0.4 mg kg^{-1}/day) prevented trichloroacetic acid-induced hepatocellular carcinoma male Sprague-Dawley rats owing to its antioxidant and anti-inflammatory effects[62]. The pleiotropic effects of CoQ10 showed that it possesses non-skeletal benefits that could benefit the ageing population by preventing multiple non-communicable disorders at the same time.

CONCLUSION

Majority of the studies reviewed agree that CoQ10 supplementation protects bone health by increasing osteoblastogenesis and reducing osteoclastogenesis, through lowering inflammation and oxidative stress in the body. However, whether these data are translatable to humans remains a question due to the lack of corresponding human studies. Therefore, further well-planned randomized control trial should be carried out to confirm the effectiveness of CoQ10 supplementation on bone health.

SIGNIFICANCE STATEMENT

This manuscript reviewed the effect Coenzyme Q10 (CoQ10) that could be beneficial for bone health. The CoQ10 is a natural antioxidant and anti-inflammatory agent generated endogenously or obtained through diet. It has been shown to protect skeletal health in animal models of osteoporosis. Previous evidence also suggests that CoQ10 modifies the RANKL/OPG dynamic to regulate the differentiation of osteoclasts to prevent bone resorption. It also affects NFκB in osteoclasts and PTEN/PI3K/AKT signalling in osteoblasts to modulate their differentiation. We summarize these findings in this review to present a comprehensive overview of the skeletal protective effects of CoQ10 to the readers. We believe that this study will garner the attention of researchers working in this field and receive many citations.

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