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Review Article

Potential roles of vitamin E in age-related changes in skeletal muscle health

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ABSTRACT

Skeletal muscle disorders including sarcopenia are prevalent during the complex biological process of aging. Loss of muscle mass and strength commonly seen in sarcopenia is induced by impaired neuromuscular innervation, transition of skeletal muscle fiber type, and reduced muscle regenerative capacity, all attributable to chronic inflammation, oxidative stress, and mitochondrial dysfunction. Current literature suggests that vitamin E molecules (α-, β-, γ-, δ-tocopherols and the corresponding tocotrienols) with their antioxidant and anti-inflammatory capabilities may mitigate age-associated skeletal dysfunction and enhance muscle regeneration, thus attenuating sarcopenia. Preclinical and human experimental studies show that vitamin E benefits myoblast proliferation, differentiation, survival, membrane repair, mitochondrial efficiency, muscle mass, muscle contractile properties, and exercise capacity. Limited number of human cross-sectional observational studies reveal positive associations between serum tocopherol level and muscle strength. Several factors, including difficulties in validating vitamin E intake and deficiency, variations in muscle-protective activity and metabolism of diverse forms of vitamin E, and lack of understanding of the mechanisms of action, preclude randomized clinical trials of vitamin E in people with sarcopenia. Future research should consider long-term clinical trials of with adequate sample size, advanced imaging technology and omics approaches to investigate underlying mechanisms and assess clinically meaningful parameters such as muscle strength, physical performance, and muscle mass in sarcopenia prevention and/or treatment.

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Article Outline

1. Introduction

Sarcopenia, the degenerative loss of muscle mass and strength associated with aging, usually starts in the fifth decade of life [1-3]. The Report of the European Working Group on Sarcopenia in Older People defines sarcopenia as the combination of low muscle mass (eg, >2 standard deviations below the mean of young adults, aged 18–39 years in same sex and ethnic background) and either low muscular strength (eg, handgrip strength <30 kg in men or <20 kg in women) or low physical performance (eg, gait speed <1 m/s in men or <0.8 m/s in women) [2]. The prevalence of sarcopenia is 5% to 13% in the population aged 60–70 years and 11%–50% in that >80 years [4]. According to the World Health Organization, by 2050, about 2 billion people worldwide will be 60 years or older, and approximately 400 million will be 80 years or older [1], making sarcopenia a potentially serious health issue.

Sarcopenia can affect mobility in the elderly, increase the risk of hospitalization and health care cost, and create a large economic burden for the society. A cohort study found that the average length of hospitalization for elderly sarcopenic patients (13.4 days) due to acute injuries or illness was 4 days more than those without sarcopenia (9.4 days) [5]. The prevalence of readmission (27%) for elderly patients with sarcopenia is much higher than that (10%) for non-sarcopenia patients; the former is accompanied by an increased mortality rate at the 6-month follow-up [5]. The prevalence of sarcopenia is 64.2% in older men and 31.3% in older women, while the population attributable risk for physical disability due to moderate and severe sarcopenia is 85.6% in older men and 26% in older women [6,7].

Sarcopenia is not fully preventable, but understanding age-associated alterations in skeletal muscle is fundamental to improve the overall quality of life, and thus to reduce the economic burden for those affected by sarcopenia. Recent studies suggest that vitamin E, a collective term for tocopherols and tocotrienols, may play an important role in the skeletal muscle health and have great potential for mitigating the progression of sarcopenia [8,9]. In this review, we summarize the cellular, animal, epidemiological and observational studies and clinical trials of tocopherols and tocotrienols in skeletal muscle health, discuss their potential mechanisms of action, and explore future directions of translational research on vitamin E and sarcopenia. The review was conducted by a literature search of PubMed, Medline, and Google Scholar databases for publications on vitamin E and skeletal muscle using keywords including cell, myoblast, animal, human, muscle atrophy, muscle strength, and sarcopenia. We hypothesize that supplementation of tocopherols and tocotrienols attenuates sarcopenia by mitigating oxidative stress and inflammation while enhancing muscle regenerative capacity.

2. Skeletal muscle anatomy and pathophysiology

Skeletal muscles constitute 45% to 55% of the total body mass and play critical roles in the movement, posture, and regulation of metabolism [10]. Skeletal muscles are classified by their contractile properties (slow twitch vs. fast twitch), myosin heavy chain isoforms (type I and II), enzymatic activities, and metabolic characteristics [10]. Slow twitch (type I) fibers exhibit lower force-generation capacity, longer time-to-peak-tension-generation and lower shortening velocity than fast-twitch (type II) fibers [10]. Slow twitch, type I fibers contain large amount of myoglobin, capillaries, lipids, and mitochondria and largely depend on oxidative phosphorylation [11]. Fast twitch, type II fibers are classified into type IIa, IIx(d) and IIb based on kinetic properties in the order of fast to fastest shortening velocity (IIa < IIx(d) < IIb) [12]. Type IIa fibers are intermediate fibers using both oxidative and glycolytic pathways to generate energy, while type IIx(d) and IIb are glycolytic fibers [13]. In addition, type I fibers are mainly recruited for daily activities and during light exercise, while type II fibers are recruited when muscles are required to generate greater force, such as high-intensity exercise [13]. While rodents express all fiber types (ie, I, IIa, IIx(d), and IIb), humans do not express IIb fibers [10]. Skeletal muscle is largely hybrid fibers [14], co-expressing a mixture of several different myosin heavy chain isoforms within the muscle. For examples, soleus muscle, located deep within the calf of the leg, consists primarily of type I fibers supplemented with type IIa fibers. Plantaris muscle, located in the superficial posterior compartment of the leg, consists primarily of type IIb fibers with small portions of type I and IIa fibers [15]. Gastrocnemius, large posterior muscle of the calf, and vastus lateralis muscle, a muscle in the thigh, are mixtures of type I, IIa, and IIx fibers [16].

Sarcopenia is induced by multiple factors including muscle atrophy, skeletal muscle fiber type transitions, and impaired muscle regenerative capacity [7,17-19]. From birth to the age

of 30, skeletal muscles grow and develop since protein synthesis rate is higher than protein degradation rate. Aging is associated with progressive decline in muscle mass, cross-sectional area, fiber numbers, and function [4-7,17]. Muscle mass decreases by approximately 12.9% in men and 5.3% in women per decade and is accompanied by a decrease in muscle strength for both sexes (10–15% in men, 2% in women per decade) [2,8]. A 5-year longitudinal study of older adults demonstrates that muscle weakens at a substantially faster rate than muscle mass loss, and gaining muscle mass does not fully prevent age-associated loss of muscle strength [20]. Therefore, age-associated loss of muscle strength, often called dynapenia, is not solely from loss of muscle mass.

The neuromuscular junction, a chemical synapse between a branch of a motor neuron and muscle fiber, initiates muscle contraction [9]. With aging, the number of motor neurons gradually decreases [10] and muscle denervation, particularly in type II motor unit, increases with collateral reinnervation of type I muscle fibers [21,22]. Satellite cells are muscle stem cells that typically remain quiescent in adult muscle [23]. When muscle cells undergo injury or damage, satellite cells play an important role in the regeneration of muscle cells [12]. The decreased number of satellite cells and their failure to sustain quiescent state in type II fibers also contribute to age-associated loss of type II fibers [20,24], including decreased shortening velocity at a given load and decreased power output properties [25].

At the level of the individual muscle fiber, sarcopenia is associated with the atrophy of type II fibers whereas type I fibers remain much less affected [26-28]. Within type I fibers, the maximal force generation and velocity are decreased with aging [29]. A previous study of human muscle biopsy samples demonstrate that significantly decreased transcript levels of type IIa and IIx, but not type I, attribute to lower synthesis rates of type II fibers with age [30]. Although type I fibers largely rely on oxidative metabolism, type II fibers generate more free radicals for every oxygen molecule used compared to type I fibers [11,31]. Once type II fibers are damaged, they are harder to regenerate due to satellite cell dysfunction in aged muscle. Satellite cells are muscle stem cells that typically remain quiescent in adult muscle [23]. When muscle cells undergo injury or damage, satellite cells play an important role in the regeneration of muscle cells [12]. The decreased number of satellite cells and their failure to sustain quiescent state in type II fibers contribute to age-associated loss of type II fibers [20,24], including decreased shortening velocity at a given load and decreased power output properties [25].

Increased oxidative stress, inflammation, and mitochondrial dysfunction contribute to neuromuscular denervation, particularly in type II fibers and muscle fiber death [32]. Free radical damages can trigger pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α). A low-grade pro-inflammatory state, manifested by higher concentrations of pro-inflammatory cytokines and acute phase proteins, is common among older adults, suggesting that the proinflammatory state may have a long-term consequence of age-associated muscle atrophy and lower function in the elderly [13]. Increased oxidative stress and inflammation in the muscle contribute to structural and functional changes of mitochondria, the important organelle for energy supply, redox regulation, and apoptosis [33]. Furthermore, mitochondrial dysfunction leads to impaired motor neuron, neuromuscular and satellite dysfunction and atrophy of type II fibers [32,34-36]. For example, sedentary elderly subjects, in contrast to highly trained elderly subjects, produce a gene profile that is consistent with elevated oxidative stress, which leads to mitochondrial dysfunction of muscle [37]. Moreover, peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), a master regulator of mitochondrial biogenesis, significantly decreases in the soleus muscle of old rats [38,39] and vastus lateralis muscle of older subjects (>65 years) compared to young subjects [37]. The complex changes in mitochondrial morphology (increased fusion and/or decreased fission) with age could interfere with mitochondrial function and mitophagy [35]. Mitochondrial DNA deletion, mutation, and the concurrent development of electron transport chain abnormalities lead to apoptosis and necrosis, contributing to muscle fiber atrophy, breakage, fiber loss, as well as motor neuron death [40]. Thus, restoring oxidative balance, and alleviating inflammation and mitochondrial dysfunction may prevent or delay the onset of sarcopenia [41]. Recently, vitamin E has gained attention for its potential impact on sarcopenia due to its antioxidant and anti-inflammation properties [42,43].

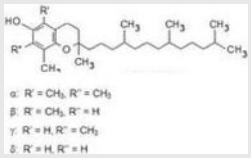
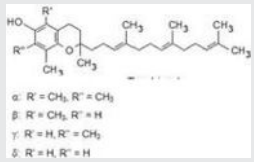
3. Absorption, distribution, metabolism, and excretion of vitamin E

Tocopherols and tocotrienols are two subgroups of vitamin E with a common chromanol ring and a saturated or unsaturated side chain, respectively [44] (Table 1). Each subgroup has four isomers (α, β, γ, and δ). All plant species contain tocopherols, whereas tocotrienols can only be found in certain plants such as annatto, palm, grains, nuts, and rubber [45-47]. The majority of the studies on vitamin E bioavailability and metabolism were conducted in mice [48], rats [49-51], hamsters [52] and humans [53,54].

Table 1 compares tocopherols and tocotrienols for structure, dietary source/supplement, absorption, metabolism, circulation, and distribution. Fig. 1 depicts the metabolism pathways of dietary α-tocopherol primarily in hepatocytes and the circulation system [55-63]. Absorbed tocopherols are largely stored in adipose tissue, and soare in liver, heart and skeletal muscle (adipose tissue > > skeletal muscle > liver > heart) [64]. Most vitamin E is located in the mitochondrial fractions and in the endoplasmic reticulum due to fat solubility. Tocopherols are metabolized by cytochrome P-450 via ω-oxidation, followed by β-oxidation in the mitochondria or by conjugation [65,66]. Tocopherol metabolites can be excreted into bile, urine or feces for elimination in animals [67-69].

Similar to tocopherols, tocotrienols are also solubilized in mixed micelles or an emulsion for small intestine uptake [70], followed by secretion via triacylglycerol-rich chylomicrons into the lymphatic system before entering blood circulation [71]. The absorption of tocotrienols is found to be more rapid than tocopherols [72]. The unsaturated side chain of tocotrienols renders themselves more lipophilic compared to tocopherol, making it easier for them to be assimilated into the cell membrane [73]. Tocotrienols accumulate in tissues

Table 1 – Comparison between tocopherols and tocotrienols

	TOCOPHEROLS	TOCOTRIENOLS
STRUCTURE [44]		
	Chromanol ring and 16-carbon hydrophobic chain	
SIDE CHAIN [44]	Long, saturated phytyl side chain; may impede the functional properties of the vitamin.	Short, unsaturated isoprenoid side chain with 3 double bonds; may facilitate various functions within the body.
DIETARY SOURCES [45-47]	Occurs often in many foods, including palm oil, rice bran, wheat germ, vegetable oils (corn, soybean, safflower, sesame), peanut oil, cocoa butter and nuts (walnuts, pecans, peanuts). Mainly α- and γ-tocopherol.	Found in low concentrations in certain foods such as palm oil, cereal grains, wheat germ, palmetto, barley, oats, rye, rice, and bran.
SUPPLEMENT	Used in multivitamins (mainly α-tocopherol) and cosmetic products (soaps, creams, make-up and hair care) as an antioxidant stabilizer.	Rarely used.
ABSORPTION	Absorbed in the intestine by means of dietary fat and secreted with chylomicron particles rich in triacylglycerol and cholesterol, which undergo lipolysis [71].	
	Uptake involves slower diffusion compared to tocotrienols [72].	Uptake involves simple diffusion mechanism; faster compared to tocopherols [71]
LIVER METABOLISM	The remaining vitamin E bound to chylomicron remnants is taken up by the liver. α-TTP transfers them to various lipoproteins in circulation. Tocopherols have much higher affinity for α-TTP than tocotrienols [71].	
CIRCULATION	Transported via TRP-containing chylomicron, VLDL, LDL, HDL. Chylomicron-bound vitamin E are largely transported to peripheral tissues via LPL followed by simple diffusion or LDL receptor-mediated uptake of LDL [71].	
	At postprandial, high concentrations are found in LDL and HDL [53].	At postprandial, high concentrations are found in TRP and HDL initially and then mainly in HDL [53].
PERIPHERAL DISTRIBUTION	High in lung, spleen and liver and lower levels in skin, muscle, and brain [51].	High in adipose tissue and skin epidermal fat but also present in plasma and various tissues including liver, kidneys, lungs, muscle and heart at lower levels [50,51].
	High levels of tocotrienols have been found in the spleen, kidney, small intestine and colon compared to tocopherols but similar levels were seen in the lungs and liver. Tocopherol and tocotrienol levels in the liver are influenced by the uptake of different forms of the vitamin taken together [70].	

Abbreviation: HDL, high-density lipoproteins; LDL, low-density lipoproteins; LPL, lipoprotein lipase; TRP, triacylglycerol-rich particle; α-TTP, α-tocopherol transfer protein; VLDL, very low-density lipoproteins.

and organs high in fat, such as epididymal fat, perirenal fat [53,54,74], skin [50], and brain [54]. A preliminary study showed that muscle tocotrienol level was <1.4 nmol/g after rats were fed a diet containing 50 mg tocotrienol/kg for 8 weeks [49], although it is not clear whether higher doses may lead to higher levels of tocotrienol in muscle.

It was noted that the bioactivity of vitamin E varies in different conditions and there are potential counteractions among the vitamin E isomers. In fact, this interplay exists among tocopherol isomers as well. α-Tocopherol supplementation at large doses has been reported to reduce the availability and benefits of γ-tocopherol that are not shared by α-tocopherol [75].

4. Actions of tocopherols on skeletal muscle from cellular, animal, and human studies

Table 2 summarizes the effects of tocopherols on skeletal muscle in cellular, animals, and human studies. In vitro studies demonstrate that α-tocopherol prevents myoblast from atrophy [76,77] and improves myotube survival [77]. α-Tocopherol

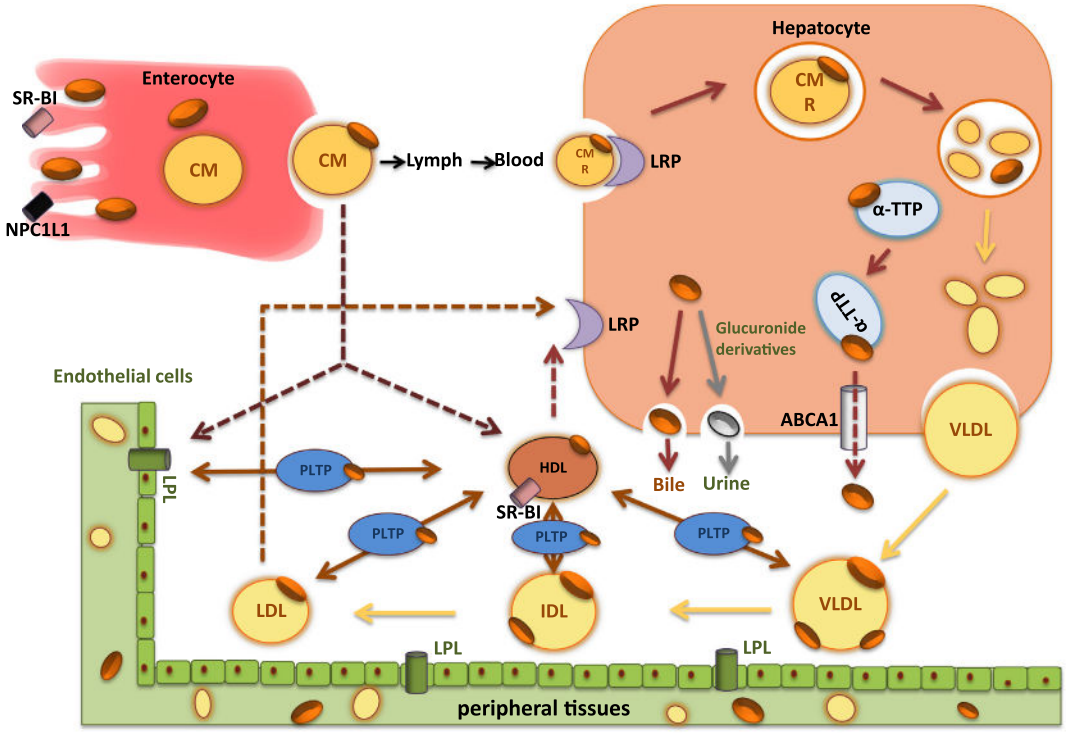


Fig. 1 – The absorption, transport, metabolism and excretion of vitamin E. Following absorption, vitamin E is incorporated into chylomicron in enterocytes. After secretion, LPL facilitates the peripheral tissues' uptake of vitamin E released from chylomicron. Chylomicron remnant is then taken up by the liver where vitamin E is integrated into nascent VLDL and secreted to the circulation for further delivery to the peripheral tissues. The affinity of vitamin E isomers for α-TTP determines their bioavailability. Cytochrome P-450 in the liver catalyzes the oxidation of vitamin E isomers prior to their urine excretion. Bile excretion of vitamin E increases with excess intake. Abbreviations: ABCA1, ATP-binding cassette transporter 1; CM, chylomicrons; CMR, chylomicron remnants; LPL, Lipoprotein lipase; LDLR, LDL receptor; NPC1L1, Niemann-Pick C1-Like 1; PLTP, Phospholipid transfer protein; SR-BI, Scavenger receptor class B type I; α-TTP, α-tocopherol transfer protein.

administration promotes membrane repair when myoblasts were exposed to an oxidant challenge induced by a laser [78]. The effects of α-tocopherol have also been tested on skeletal muscle in a variety of animal models, including diabetes [79], ischemia–reperfusion [80], and muscle atrophy induced by hindlimb unloading [81,82]. Animal studies show that α-tocopherol supplementation improves antioxidant defense [80], decreases oxidation [80,81], suppresses oxidative stress [79], increases protein synthesis [79], and decreases protein degradation [81]. Oxidative stress biomarkers such as H_2O_2, a byproduct of lipid peroxidation (ie, thiobarbituric acid-reactive substance, TBARS) and malondialdehyde (MDA) and protein oxidation [81] were reduced in tocopherol-treated animals, whereas antioxidants such as glutathione/glutathione disulfide (GSH/GSSG), superoxide dismutase (SOD), and catalase (CAT) were up-regulated [79-81]. In addition, inflammatory markers such as TNF-α and IL-1β were down-regulated by tocopherols in animals [79-81].

In cross-sectional studies, higher tocopherol status, represented by plasma α-tocopherol level, is associated with greater strength measures (eg, grip and knee strength) in elderly women (70–70 y) [83] and the lower tendency of frailty in elderly women and men (≥65 y) [84,85]. A 3-year follow-up Invecchiare in Chianti (InCHIANTI) longitudinal study of 698 community-living, apparently-healthy women and men (≥65 y) [86] found that (i) after adjusting for potential confounders, only low serum α-tocopherol level (<24.9 μmol/L) was significantly associated with a subsequent decline in physical function; (ii) the baseline serum α-tocopherol level was significantly associated with physical function at 3-year follow-up; and (iii) α-tocopherol was the most important determinant for the decline in physical function of subjects (≥81 y) [86]. These observational findings have indicated that α-tocopherol supplementation may improve muscle function or mitigate functional decline during aging, which might be in part mediated by suppression of oxidative stress and inflammation as supported by animal studies.

Tocopherol plays different roles in various muscle fibers. Meydani et al [87] reported that there is an inverse relationship between plasma α-tocopherol concentration and the percentage of type I muscle fibers in healthy adults (21–44 y) after 30 days of α-tocopherol (800 IU/day) supplementation. In Meydani's study [87], individuals with a larger composition of type I fibers may utilize more α-tocopherol to prevent contractile activity-induced oxidative damage [88], since type I fibers heavily rely on oxidative metabolism. Similarly, growing swine fed selenium-vitamin E deficient diets had selective atrophy of type I fibers and displayed decreased phosphorylase activity in type II fibers [89]. Supplementation of α-tocopherol prior to and during the phase of muscle

Table 2 – Effects of tocopherols on skeletal muscle health from cellular, animals, and human studies

First Author, Year [ref]	Experimental design and treatment	Parameters	Results
In vitro studies			
Frati, 2014 [76]	Pretreatment with γ-tocopherol (24 nM) or total tocopherols in atrophic C2C12 myotubes, induced by starvation or dexamethasone.	Atrophy	↓ Cell atrophy via ↑ cell diameter and myonuclei number. ↑ Protein synthesis and ↓ Expression of E3 ubiquitin ligase (MAFbx/atrogin-1).
Von Grabowiecki, 2015 [77]	Pretreatment with tocopherols (1 nM-125 μM) in atrophic C2C12 myoblast, induced by cytotoxic agents.	Atrophy	Dose dependent in survival. ↑ Cell survival by protecting against oxidative and DNA damage-induced stresses. ↓ Notch expression pathway, negative regulator of cell regeneraton (ie, Notch1, Notch3, and Hes1) in stressed myoblasts.
Howard, 2011 [78]	Pretreatment α-tocopherol (200 μM) in injured C2C12 myoblasts, induced by laser wounding.	Injury	↑ Plasma membrane repair and survival in mechanically injured myoblast.
Animal studies			
Aragno, 2004 [79]	Streptozotocin-induced diabetic model in male rats. α-Tocopherol (400 mg/kg BW) was given for 21 days in	Oxidative stress and muscle protein synthesis in gastrocnemius	↓ H_2O_2 levels and oxidative stress (↑ GSH/GSSG). ↑ Target genes regulating protein synthesis and muscle repair.
Dong, 2014 [80]	Hind limb ischeumia model. α-Tocopherol (10 mg/kg BW) via IP was given 1 hour before reperfusion in rats undergoing 4 hours hind limb ischemia followed by 2 hours reperfusion.	Antioxidant enzymes in gastrocnemius; Plasma inflammatory mediators	↑ GSH, SOD, and CAT. ↓ MDA and protein oxidation ↓ Plasma levels of TNF-α and IL-1β.
Servais, 2007 [81]	Hindlimb unloading (HU)-induced soleus muscle atrophy model in Wistar male rats. Prior uploading, control and α-tocopherol (60 mg/kg IP, 2×/wk) for 21 days. Then, control, α-tocopherol (60 mg/kg BW, IP, 2×/week), HU, and HU+α-tocopherol for 14 days.	Atrophy, oxidative stress, and muscle proteolysis in soleus	↑ Muscle mass and type I and IIa fiber cross-sectional area. ↓ Muscle proteolysis by ↓ expression of calpains, caspases-3, –9, and –12, E3 ubiquitin ligases (MAFbx and MuRF1). ↓ TBARS. ↔ Antioxidant enzyme activities (ie, SOD, CAT, GPX).
Koesterer, 2002 [82]	Hindlimb unloading (HU)-induced soleus muscle atrophy model in SD female rats. Prior uploading, control and α-tocopherol (30 mg/kg IP daily) for 7 days. Then, control, α-tocopherol (30 mg/kg bw, IP, every other day), HU, and HU+α-tocopherol for 14 days.	Antioxidant enzymes, muscle protein, and muscle mass	Relative to the HU group, HU+α-tocopherol group: ↔ Soleus and gastrocnemius mass and protein concentration. ↑ Antioxidant capacity of muscle.
Human cross-sectional observational studies			
Semba, 2003 [83]	699 women (70–79 years) in Women's Health and Aging Studies.	Muscle strength	Strong positive association between plasma α-tocopherol and strength measures (grip strength and knee strength).
Semba, 2006 [84]	766 women (65 and older) from Women's Health and Aging Studies.	Fraility	Women in the lowest quartile of serum α-tocopherol had an increased risk of becoming frail, after adjusting for age, smoking status, and chronic pulmonary disease.
Ble, 2006 [85]	Cohort study (InCHIANTI study). 827 wome and men, ≥65 years free from dementia and disability.	Fraility	Highest α-tocopherol tertile were less likely to have frail syndrome (self-reported weight loss, low energy, slow gait speed, low grip strength, and low physical activity) than were participants in the lowest α-tocopherol tertile.

Table 2 (*continued*)

First Author, Year [ref]	Experimental design and treatment	Parameters	Results
Bartali, 2008 [86]	Cohort study with a 3-year follow-up assessment on physical function. 698 women and men, ≥65 years.	Physical Function	A low concentration of α-tocopherol was significantly associated with subsequent decline in physical function (4-meter walking speed, repeated chair rises, standing balance).
Human experimental studies			
Meydani, 1997 [87]	Design: Pre and post-test. Treatment: 9 healthy adults (21–44 y) on α-tocopherol (800 IU/day) for 30 days.	Plasma and gastrocnemius muscle; BMI; Muscle fiber type	↑ α-Tocopherol & ↓ γ-tocopherol in plasma and gastrocnemius muscle. Muscle α-tocopherol was inversely correlated with BMI. The percentage of type I fibers was inversely correlated with plasma α-tocopherol, not muscle α-tocopherol.
Meydani, 1993 [88]	Design: Double-blinded placebo-controlled design in young men (n = 9, 22–29 y) and old sedentary men (n = 12, 55–74 y). Treatments: α-tocopherol+ γ-tocopherol (800 IU/day) for 48 days. A bout of eccentric exercise before samples collection.	α-Tocopherol levels; Lipid peroxidation	Relative to placebo group, the α-tocopherol+γ-tocopherol group: ↑ α-Tocopherol in plasma and skeletal muscle. ↓ Urinary TBARS. ↓ Muscle lipid conjugated dienes.
Sacheck, 2003 [92]	Design: Randomized controlled trial in active young men (n = 16, 18–35 y) and older men (n = 16, 65–80 y). Treatments: placebo and α-tocopherol (1000 IU/day) for 12 weeks. Blood was collected before, immediately postexercise (0 h), and at 6, 24, and 72 hours.	Cell damage; Lipid peroxidation	Compared to the placebo, α-tocopherol supplementation: ↓ CK in young but not in older men after exercise. ↓ F2α-isoprostanes in older men in both resting state and after exercise.
Santos, 2016 [93]	Design: Pre- and post-test. Treatment: 9 healthy young men (24.2±2.2 y) performed 3 sessions of 60 min of exercise (70% maximal oxygen uptake) interspersed for 1 week under normoxia, hypoxia, and hypoxia after α-tocopherol (250 mg) supplementation 1 hour before exercise. Blood was collected before, immediately after and at 1 hour after exercise.	Cell damage; Inflammation	α-Tocopherol supplementation: ↓ CK, LDH. ↓ TNF-α, IL-10, IL-6 after moderate exercise in hypoxia.

Abbreviations: BW, body weight; BMI, body mass index; CAT, catalase; GPX, glutathione peroxidase; GSH, glutathione; GSSG, oxidized glutathione; IL, interleukin; LDH, lactate dehydrogenase; MDA, malondialdehyde; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substance; TNF-α, tumor necrosis factor-α.
↑ increase; ↓ decrease; ↔ no difference.

atrophy reduces hindlimb-induced slow twitch muscle (ie, soleus) atrophy, resulting in increased type I and IIa muscle fiber size and decreased muscle proteolysis rate [81]. Furthermore, tocopherol has been shown to influence the composition and metabolism of lamb muscle lipids by regulating transcription of genes related to lipid metabolism in the muscle [90,91]. These studies strongly suggest that the lower serum concentration of vitamin E in older subjects may further accelerate muscle function deterioration in aged populations having a larger composition of type I fibers than type II fibers. Thus, vitamin E deficiency is likely to affect the daily living of the elderly. In summary, we can speculate that vitamin E's antioxidant and anti-inflammatory properties may suppress free radical generation, and thus may attenuate type II fiber damages and loss of type II fibers, while mitigating type I contractile dysfunction.

Changes in activity levels have great impact on skeletal muscle. Muscle hypertrophy has been associated with resistance exercise or anabolic agent administration, whereas muscle atrophy has been observed under conditions such as

starvation, aging, and physical inactivity. A study by Meydani's group found that α-tocopherol supplementation at a dose of 800 IU for 48 days reduced the expression of oxidative stress markers in both young (22–29 y) and old (55–74 y) sedentary men [87]. A longer supplementation period of α-tocopherol (12 weeks) decreased F2α-isoprostanes and had no impact on creatinine kinase (CK) in both resting and post-exercise states in older men (65–80 y), suggesting that α-tocopherol reduces muscle damage by protecting against exercise-induced oxidative stress [92]. In a recent pre- and post-test study, Santos et al reported that α-tocopherol supplementation 1 hour before exercise under hypoxia condition reduced cell damage (manifested by decreased CK and lactate dehydrogenase) and inflammation (decreased TNF-α, IL-10, and IL-6) in healthy young men (24.2± 2.2 y) [93].

In summary, all studies show beneficial effects of tocopherols in various pathophysiological models (ie, hindlimb suspension, exercise, and ischemic-perfusion injury) by decreasing oxidative stress, inflammation, atrophy while increasing regenerative capacity.

5. Actions of tocotrienols on skeletal muscle from cellular, animals, and human studies

Table 3 summarizes the effects of tocotrienols and tocopherols on skeletal muscle health. In a stress-induced premature senescence myoblasts model, low dose of palm oil-derived tocotrienols-rich fraction (TRF, consisting of 70% of α-, β-, and γ-tocotrienol and 30% of tocopherols) stimulates myoblast proliferation, but a high dose of TRF was cytotoxic [94]. TRF attenuates senescence as shown by a decrease in senescence-associated β-galactosidase (SA-β-gal) in primary human myoblasts, suggesting that TRF may replenish the regenerative capacity of myoblasts [94]. Recently, Khor et al [95] reported that relative to the vehicle group, both α-tocopherol and TRF treatments help regain the morphology of young cells, improve cell viability, and decrease SA-β-gal expression in senescent myoblasts. TRF, but not α-tocopherol, increased BrdU incorporation in senescent myoblasts and promoted myogenic differentiation by impacting the expression of myogenic regulatory factors [95], suggesting that tocotrienols promote myoblasts proliferation. Tocotrienols (0–16 μM) are also shown to inhibit inflammation by decreasing 20S proteasome activity [96].

Reduced antioxidant capacity in skeletal muscle, often associated with obesity [97,98], has been suggested to cause impairment in insulin signaling, insulin resistance, type II diabetes [98,99], and reduced exercise tolerance shown in obese humans and animals [100,101]. Tocotrienols improved exercise endurance capacity, such as increased total distance run in diet-induced obese rats, but had no impact on glucose tolerance, adiposity, and insulin sensitivity [102]. Both α-tocopherol and TRF supplementation significantly decreased protein oxidation in type IIa and IIb fibers after a single bout of strenuous exercise that induces lipid damage in skeletal muscle [103]. Tocotrienols supplementation ameliorates jumping exercise-induced deteriorating muscle contractile function and fatigue in gastrocnemius muscle of rats by enhancing antioxidant capacity [104]. In a forced swimming study, TRF, not α-tocopherol, was shown to enhance exercise tolerance (in terms of swimming time), attenuate muscle and liver glycogen use, and reduce the increase in plasma lactic acid levels in rats during exercise, suggesting that TRF enhanced fat oxidation and thus reduced carbohydrate oxidation [105]. These TRF-treated rats also showed significantly higher activity levels of endogenous antioxidant enzymes, such as SOD, CAT, and glutathione peroxidase (GPX) in liver and muscle relative to the control group [105]. In addition to suppressing oxidative stress, tocotrienols alleviate mitochondrial dysfunction [106]. Fang et al [107] demonstrated that α- and γ-tocotrienol, not tocopherol, activated peroxisome proliferator-activated receptors α, γ, and δ (PPARα, PPARγ, and PPARδ) and PPAR target genes [107] that play essential roles in energy metabolism, mitochondrial biogenesis, and skeletal muscle fiber distribution [108].

In a randomized, double-blinded, placebo controlled trial, supplementation of TRF (160 mg/day, containing 74% tocotrienols and 26% tocopherols) for 6 months markedly lowered protein carbonyl levels and advanced glycosylation end products in those 50 years and older. Beneficial changes in antioxidant enzyme activities, including SOD, CAT, and GPX due to TRF, were more marked in older adults [109]. In the same study, TRF supplementation was also shown to be more beneficial to the older group than the young group by reducing DNA damage, as manifested by a reduction in urinary 8-hydroxy-2′-deoxyguanosine (an DNA damage oxidative stress marker) [110].

In summary, tocotrienols have been shown to stimulate myoblast proliferation and improve exercise capacity in both sedentary and exercised animals by decreasing oxidative stress and increasing antioxidant capacity. All studies suggest that older adults would benefit from tocotrienols supplementation for their skeletal muscle health. Further study is needed to investigate the effects of tocotrienols - instead of mixtures of tocopherols and tocotrienols - on skeletal muscle properties, including muscle mass, fiber type, and muscle function in the elderly with sarcopenia.

6. Possible mechanisms

Up-regulated oxidative stress and inflammation play critical roles in age-associated skeletal muscle dysfunction (sarcopenia) [111,112]. Activation of the transcription factor NF-κB has been closely implicated in redox signaling [113,114] and inflammation [115,116]. Reactive oxygen species damage membranes including mitochondrial membrane and endoplasmic reticulum, where vitamin E tends to exist in abundance due to its hydrophobicity. If sufficient vitamin E is present in the injured muscle plasma membrane, muscles can repair and survive from the injury [78]. Vitamin E including tocopherols and tocotrienols is able to lower oxidative stress by inducing higher concentrations of endogenous antioxidant enzymes (such as SOD, CAT, and GPX), and reducing blood lactate, plasma glutathione S-transferase (GST), plasma and liver TBARS, and liver and muscle protein

Table 3 – Effects of tocotrienols and tocopherols on skeletal muscle health from cellular, animal, and human studies

First Author, Year [ref]	Experimental design and treatment	Parameters measured	Results
In vitro studies			
Lim, 2013[a] [94]	Stress-induced premature senescence by 1 mM H_2O_2 in primary human myoblasts (CHQ5B). Pre- and posttreatment with tocotrienol rich fraction (TRF) at 50 μg/mL.	Regeneration	↓ Senescence and reversed myoblasts aging. ↑ Proliferation in post-treatment group, but not in pre-treatment group.
Khor, 2016[b] [95]	Primary human myoblasts underwent serial passaging to reach senescence; treated with α-tocopherol and TRF for 24 h.	Regeneration Oxidative stress	↓ Senescence and reversed myoblasts aging in α-tocopherol and TRF group. ↑ Proliferation via ↑ myogenic regulatory factors in TRF treated group but not α-tocopherol. ↓ ROS generation in TRF group (Effect: TRF > α-tocopherol).
Animal studies			
Betik, 2016[a] [102]	An exercise endurance model. Male rats (6-wk.-old). Treatment: High-fat diet with or without tocotrienols (50 mg/kg BW) for 10 weeks.	Muscle enzymes	↑ Exercise capacity (total distance ran) with unknown mechanisms. ↔ BW, adiposity, body composition, glucose tolerance, or insulin sensitivity. ↔ Plantaris muscle glycogen content or liver glycogen content. ↔ CS activity in soleus and plantaris muscle.
Reznick, 1992[b] [103]	A single bout of exercise-induced lipid damage model. Female rats. Treatments: control (30 IU α-tocopherol/kg diet), α-tocopherol (10 000 IU/kg diet), and palm oil (rich in α-tocopherol and tocotrienol, containing 7000 mg tocotrienol/kg diet) for 4 weeks.	Protein oxidation	↓ Protein oxidation in skeletal muscle (type IIa and IIb) at both resting and exercise statuses in both α-tocopherol and palm oil.
Alwan, 2011[a] [104]	A jumping exercise-induced muscle deterioration model. Male Wistar-Kyoto rats. Treatments: sedentary control, exercise control, sedentary + tocotrienols (8 mg/kg BW), and exercise + tocotrienols for 6 weeks.	Muscle contractile properties and fatigue resistance. Antioxidant enzyme activity in gastrocnemius muscles	↑ Muscle contractile properties. ↓ Exercise-induced fatigue. ↑ GPX and ↓ lipid peroxidation with tocotrienol alone or tocotrienol with exercise.
Lee, 2009[b] [105]	A forced swimming model. Young Male rats. Treatments: control, TRF25 (25 mg/kg BW), TRF50 (50 mg/kg BW), α-tocopherol (25 mg/kg BW) via gavage for 28 days.	Fuel metabolism, oxidative stress, and antioxidant enzyme activity after swimming exercise	Only TRF, not α-tocopherol: ↑ Swimming time. ↓ Usage of liver and muscle glycogen and blood lactate after maximal swimming exercise. ↓ Protein carbonyl production in liver and muscle. ↓ TBARS in plasma and liver in all groups. ↑ Total antioxidant capacity in plasma in TRF50. ↑ Antioxidant enzyme activity (SOD, CAT, GPX) in the liver in TRF50.
Human experimental studies			
Chin, 2011[a] [109]	Randomized double-blinded placebo-controlled trial in adult (35–49 y., n = 31) and older (≥50 y., n = 31). Treatment: placebo or TRF (160 mg/day) for 6 months.	Lipid profile. Oxidative stress	↑ HDL-cholesterol and tocotrienol in plasma. ↓ Protein carbonyl content. ↓ plasma AGE and SOD. ↑ Plasma GPX activity. Effect: Older > Adults.
Chin, 2008[a] [110]	Randomized double-blinded placebo-controlled trial in adult (35–49 y., n = 31) and older (≥ 50 y., n = 31). Treatment: placebo or TRF (160 mg/day) for 6 months.	Oxidative stress	↓ Total DNA damage in leukocytes. ↓ Urinary 8-OHdG in the older group only.

Abbreviations: 8-OhdG, 8-hydroxy-2-deoxyguanosine; AGE, advanced glycosylation end products; BW, body weight; CAT, catalase; CHQ5B, the satellite cells isolated from the quadriceps of a 5-day-old infant; CS, citrate synthase; GPX, glutathione peroxidase; HDL, high-density lipoprotein; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substance; TFAM, transcription factor A, mitochondrial; TRF, tocotrienol rich fraction. [a] indicates only tocotrienol study; [b] indicates comparison between tocotrienol and tocopherol. ↑ increase; ↓ decrease; ↔ no difference.

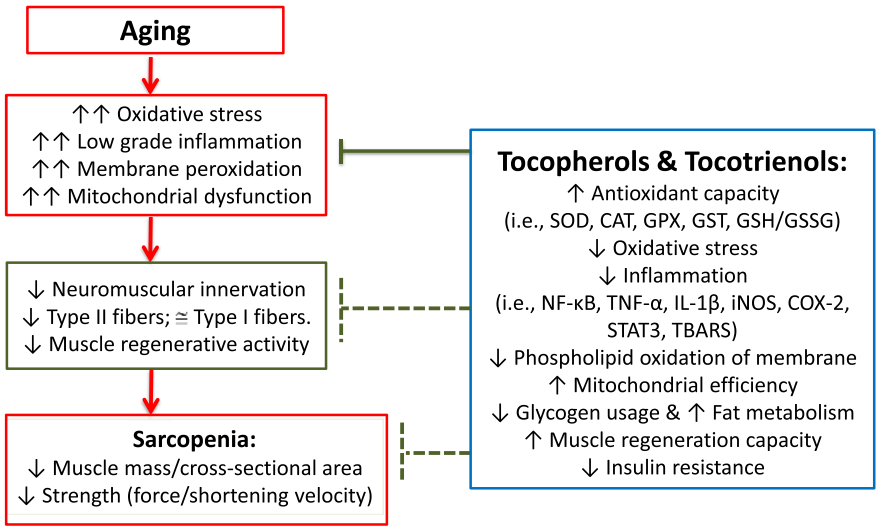


Fig. 2 – Proposed mechanisms of action of vitamin E in mitigating age-associated skeletal muscle dysfunction. Aging is associated with increases in oxidative stress, low-grade inflammation, membrane peroxidation and mitochondrial dysfunction that lead to decreases in neuromuscular innervation, type II fiber and muscle regenerative activity and eventually, sarcopenia that is characterized by reduced muscle mass and strength. Arrows indicate the sequential events causing sarcopenia, and the solid line shows the impact of vitamin E on sarcopenia-inducing events. Dotted lines show possible effects and mechanisms of action of vitamin E that await future studies. Abbreviation: CAT, catalase; COX-2, cyclooxygenase 2; GPX, glutathione peroxidase; GST, glutathione S-transferases; IL, interleukin; iNOS, inducible nitric oxide; NFκB, nuclear factor κ-light-chain-enhancer of activated B cells; SOD, superoxide dismutase; STAT-3, signal transducer and activator of transcription-3; TBARS, thiobarbituric acid-reactive substance; TNF-α, tumor necrosis factor-α.

carbonyl in a variety of oxidative stress models. Tocotrienols have been shown to suppress the expressions of inflammation mediators including NF-κB [116], TNF-α [116], IL-1 [117], IL-6 [118], IL-8 [119], inducible nitric oxide synthase (iNOS) [120], cyclooxygenase 2 (COX-2) [121,122], and STAT3 [120]. In addition, tocotrienols modulate hypoxia-induced factor-1, which is also linked to inflammation [119].

Fig. 2 illustrates the plausible mechanisms of sarcopenia and how vitamin E mitigates age-associated skeletal muscle dysfunction. Many lines of research suggest that vitamin E may slow down aging of skeletal muscle through the following possible mechanisms: 1) attenuate oxidative stress and suppress inflammation by enhancing antioxidant capacity; 2) improve membrane repair and increase survival of injured skeletal muscle by mitigating oxidized phospholipid formation; 3) improve mitochondrial energetic efficiency; 4) decrease usage of glycogen in skeletal muscle, while increase fat oxidation; 5) enhance muscle regeneration capacity; and 6) stabilize insulin structure and improve insulin sensitivity of skeletal muscle.

7. Summary, limitation, and future directions

Existing in vitro, in vivo, epidemiological, and clinical studies, albeit limited, suggest vitamin E may mitigate sarcopenia, a major skeletal muscle disorders in the elderly. Previous studies demonstrate that beneficial effects of vitamin E including antioxidant, anti-inflammatory, and regenerative activities can possibly attenuate sarcopenia. While α-tocopherol is the main ingredient in the current formulation of vitamin E, some studies suggest that tocotrienols possess a higher antioxidant capability and other antioxidant-independent biological functions not shared by tocopherols [123,124]. However, there is limited evidence regarding the difference in skeletal health between tocopherols and tocotrienols. Whether the differential mechanisms of actions of tocopherols and tocotrienols play a role in their protection against sarcopenia still remains unknown.

We noted that the doses of tocopherols used the in vitro studies are at concentrations below [77,125] and above [65,77] the physiological concentration of tocopherols in humans (approximately 20–30 μM) [126], and those used in animal and clinical studies have largely used doses exceeding the recommended dietary allowance (RDA) levels for humans. Similar patterns of doses for tocotrienols in cellar and animal studies were also observed. However, there is no established RDA level of tocotrienols for humans yet. The doses of tocopherols used in the clinical studies were well within the 1000 mg/day Tolerable Upper Intake Level of vitamin E. A recent study reported no toxicity of δ-tocotrienol at doses up to 1600 mg/day in healthy adult subjects [127]. A typical human diet is likely to provide sufficient tocopherols, but not tocotrienols. Due to the scarcity of tocotrienols in typical diet, the doses of tocotrienols used in the clinical studies may likely be achieved only with supplements. For an adult, vitamin E (α-tocopherol) RDA is 15 mg or 22.4 IU [128]. Consistent with the finding from the National Health and Nutrition Examination Survey (NHANES), that most people in U.S. consume less than the RDA level of vitamin E [129], several studies showed the high prevalence of vitamin E deficiency in the free-living American elderly population

[129,130], potentially contributing to skeletal myopathy and frailty due to loss of muscle strength.

A number of issues have challenged conducting randomized clinical trials examining the role of vitamin E supplementation in people with sarcopenia. First of all, vitamin E deficiency in terms of muscle function and sarcopenia has to be defined. Additional biomarkers for vitamin E intake, such as the ratio of α-tocopherol to total lipid or platelet α-tocopherol concentration may need to be validated for clinical practice. Second, α-tocopherol does not represent the effects of various forms of vitamin E against muscle aging. Some studies have shown the benefits of tocotrienols that are not shared by tocopherols. The selection of more effective isoforms of vitamin E on muscle health, and the optimal dosage and treatment period are all important. Finally, the molecular and cellular events driven by vitamin E in protecting sarcopenia need to be further investigated.

The existing studies have several limitations. Most available animal studies showing vitamin E-induced increases in skeletal muscle mass and strength have used young animals, which are not necessarily applicable to sarcopenia in the elderly Vitamin E-mediated modulation of satellite cell number and function and effects of anti-oxidation and anti-inflammation on age-associated motor unit denervation and type II fiber loss, currently shown in cell studies, should be extended to studies in animals and humans. Future long-term clinical trials and ultimately community interventions with adequate sample sizes are needed to illustrate the underlying mechanisms of action of tocotrienols and tocopherols, to determine the timing, doses, and appropriate methods of administration of vitamin E, and to increase the bioavailability of vitamin E, particularly tocotrienols. Assessment of vitamin E status via biomarker validation and evaluation of its efficacy using advanced imaging technology and approaches in nutrigenomics and metabolomics would further elucidate the potential of vitamin E in sarcopenia prevention and/or treatment.

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