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The Role of Choline (B4) in Muscle and Heart Health and Its Function – A Narrative Review

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Abstract

Background: Choline is an essential micronutrient critical for neurotransmitter synthesis, lipid metabolism, and cellular function. Evidence demonstrates its vital importance for skeletal muscle and cardiac function.

Objective: This narrative review analyzes choline's role in muscle and cardiac health, the biochemical mechanisms supporting muscle contraction and cardiac function, and practical implications for athletes and cardiovascular patients.

Methods: Systematic search of PubMed, Scopus, and Web of Science (2026) using keywords: choline, muscle health, acetylcholine, cardiac function, muscle contraction, cardiomyopathy and supplementation. Priority given to randomized controlled trials, mechanistic studies, and systematic reviews.

Results: Choline serves as a precursor to acetylcholine (ACh), the primary neurotransmitter for neuromuscular transmission and muscle contraction initiation [1–4]. Deficiency is associated with reduced strength and impaired nerve-muscle signaling [1,2,5–8]. Chronic deficiency decreases phosphatidylcholine synthesis, impairing muscle membrane integrity [9–11]. In cardiac health, choline and betaine lower homocysteine levels, a cardiovascular risk factor [12–14], and demonstrate cardioprotective effects through oxidative stress reduction and enhanced parasympathetic function [15–17]. Adequate intake (550 mg/day men; 425 mg/day women) is obtained through meat, seafood, eggs, legumes, and cruciferous vegetables [18–20]. Choline

supplementation may improve endurance performance during intense exercise exceeding 2 hours [21,22].

Conclusions: Choline is essential for muscle health as an acetylcholine precursor and membrane lipid component, supporting contraction and protein synthesis. For cardiac health, choline reduces disease risk by lowering homocysteine and reducing oxidative stress. Adequate choline is vital for athletic performance and may support cardiac function in cardiovascular disease patients.

Keywords: choline, acetylcholine, skeletal muscle, cardiac function, cardiomyopathy, deficiency, performance, lipid metabolism, homocysteine, sports nutrition

1. Introduction

Choline is an essential micronutrient defined by the Institute of Medicine in 1998, which the body can synthesize in limited amounts but typically requires dietary supplementation [1,2]. As a precursor to acetylcholine (ACh), the primary neurotransmitter for muscle contraction, choline plays a fundamental role in synaptic transmission, neuromuscular junction function, and skeletal muscle contraction [1,3,4]. Beyond neurological functions, choline is a component of phosphatidylcholine (PC), the primary cell membrane lipid, and serves as a methyl donor in one-carbon metabolism [2,5].

The ability of skeletal muscle to generate force and perform work depends on precise communication between motor neurons and skeletal muscle fibers through neurotransmitter action [1,3]. Disruptions in choline distribution or ACh synthesis lead to reduced muscle contractility, decreased power, and functional impairment [6,7,8]. Additionally, in cardiovascular health, choline and its metabolite betaine modulate homocysteine levels — an independent cardiovascular disease risk factor — through homocysteine-to-methionine conversion [12,13,14].

A concerning trend suggests many populations do not consume adequate choline [2,18]. Average choline intake in the United States is approximately 313 mg/day, below the Adequate

Intake (AI) of 550 mg/day for men and 425 mg/day for women [2,20]. This gap may have significant consequences for muscle and cardiovascular function, particularly in athletes performing intense exercise or individuals with existing cardiovascular disease [21,22].

Understanding mechanisms through which choline supports muscle contraction, protein synthesis, and cardiac function is essential for optimizing athletic performance, preventing cardiovascular disease, and promoting overall health through appropriate nutrient intake [1,2,12–14].

Research Objective. Synthesis of current knowledge regarding choline's role in muscle and cardiac health, assessment of biochemical mechanisms through which choline supports muscle and cardiac functions, and provision of evidence-based recommendations for athletes, patients, and clinical practitioners to optimize choline intake.

2. Choline Biochemistry and Mechanisms of Action

2.1. Structure and Metabolic Pathways

Choline [$(CH_3)_3N^+–CH_2–CH_2–OH$] is a small nitrogen-containing molecule that can be synthesized endogenously through phosphatidylethanolamine methylation in the liver, but endogenous production typically covers only 50–60% of total requirements [1,2]. Exogenous choline originates from animal products (meat, poultry, fish, dairy, eggs) and, to a lesser extent, from plant products (cruciferous vegetables, legumes, nuts, seeds) [18–20].

After absorption, choline undergoes several major metabolic pathways [1,2,5]:

Pathway 1: Acetylcholine (ACh) Synthesis. Choline is phosphorylated to phosphocholine by choline kinase, then converted to acetylcholine by choline acetyltransferase (ChAT), particularly in neurons and neuromuscular junctions [1,3]. ACh is then released into the synaptic cleft, where it binds to nicotinic receptors on muscle fibers, initiating muscle contractions [1,3,4].

Pathway 2: Phosphatidylcholine (PC) Synthesis - Kennedy Pathway. Choline enters cells through choline transporters (especially SLC44A1 in muscle), where it is phosphorylated to phosphocholine and converted to cytidine-5'-diphosphocholine (CDP-choline) and ultimately coupled with diglyceride (DAG) to produce phosphatidylcholine [9,10,11]. Phosphatidylcholine is a critical lipid in cell membranes, mitochondria, and sarcoplasmic reticulum, ensuring structural and functional integrity [9,10,11].

Pathway 3: Betaine Metabolism - Methyl Donor Function. Choline is oxidized to betaine via choline oxidase, with betaine serving as a methyl donor in homocysteine-to-methionine conversion through betaine-homocysteine methyltransferase (BHMT) [12,13,14]. This pathway is critical for homocysteine control, which at elevated levels is an independent cardiovascular risk factor [12,13].

2.2. Acetylcholine and Muscle Contraction

Skeletal muscle contraction initiates through complex nerve signal transmission to the muscle via the neuromuscular junction (NMJ) [1,3,4]:

1. **Motor neuron depolarization.** An action potential travels along the motor neuron to the presynaptic terminal.
2. **Acetylcholine release.** Ca^{2+} influx to the presynaptic terminal triggers acetylcholine release into the synaptic cleft.
3. **ACh binding to receptors.** ACh binds to nicotinic receptors on the postsynaptic muscle membrane, opening Na^{+} and K^{+} channels.
4. **Muscle membrane depolarization.** Na^{+} ion influx causes membrane depolarization and generates a muscle action potential.
5. **Ca^{2+} release from sarcoplasmic reticulum.** Action potential travels through T-tubules, opening sarcoplasmic reticulum channels and releasing Ca^{2+} into muscle cytoplasm [1,3].
6. **Actin-myosin interaction.** Ca^{2+} binds to troponin C on thin actin filaments, shifting tropomyosin and exposing myosin-binding sites. Myosin heads attach to actin, causing a power stroke that pulls thin filaments toward the sarcomere center, producing contraction [1,3].

Inadequate choline or ACh disrupts this sequence: muscle depolarization is weakened, Ca^{2+} release is decreased, and force-generating capacity is reduced [6,7,8].

2.3. Phosphatidylcholine and Muscle Membrane Integrity

Phosphatidylcholine, the primary membrane lipid, comprises ~50% of lipids in skeletal muscle membranes and is particularly abundant in mitochondrial and sarcoplasmic reticulum membranes [9,10]. Phosphatidylcholine structural integrity is critical for several muscle functions [9,10,11]:

Membrane integrity. PC constitutes a critical component of the lipid bilayer cell membrane, providing elasticity, permeability, and structural stability essential for normal cellular function.

Sarcoplasmic Reticulum Function. Sarcoplasmic reticulum stores and releases Ca^{2+} , controlling muscle contraction, and high PC content in SR membranes ensures proper Ca^{2+} channel function and SERCA pump (Ca^{2+}-ATPase) activity.

Mitochondrial function. Muscle mitochondria, whose membranes contain high PC-to-phosphatidylethanolamine (PE) ratios, are optimized for energy production through oxidative phosphorylation.

Choline deficiency decreases PC synthesis, leading to membrane instability, impaired ion mobility, and sarcoplasmic reticulum dysfunction — all contributing to reduced contractile capacity and muscle function [9,10,11].

3. Choline and Skeletal Muscle Health

3.1. Neuromuscular Junction Function

Proper neuromuscular junction (NMJ) function — the synapse between motor neurons and muscle fibers — depends absolutely on adequate choline reserves and ACh production [1,3,4]. Research shows muscles with low choline concentrations exhibit impaired neuromuscular transmission, reduced force generation rates, and decreased performance [6,7].

In animal studies, choline-deficient diets decreased ACh levels and caused NMJ dysfunction, manifesting as reduced contractile power, decreased muscle activation speed, and impaired coordination. Conversely, choline supplementation restored NMJ parameters toward normal values, improving muscle performance [6,7].

In humans, individuals with low choline intake showed reduced handgrip strength, decreased physical work capacity in ergometer tests, and diminished resistance exercise performance [8]. In a prospective study of middle-aged adults (50–69 years), those with low choline intake (~51% AI) demonstrated significantly smaller strength gains following 12 weeks of resistance training compared to those with higher choline intake (~68–118% AI) [8].

3.2. Muscle Protein Synthesis and Hypertrophy

Choline, as a methyl donor through betaine, plays a role in regulating muscle protein synthesis [2,5,6]. Choline deficiency reduces S-adenosylmethionine (SAM) availability, the universal methyl donor, disrupting protein metabolism by decreasing protein translation and anabolic pathway activation [5,6].

Animal studies showed choline-deficient diets decreased skeletal muscle protein content, especially in energy-demanding muscles. Chronic choline deficiency significantly reduced muscle protein content, causing growth and function impairment [5,6].

In an older adult study involving resistance training, those with higher choline intake showed greater strength gains, though not necessarily greater muscle mass increases. This suggests choline may indirectly affect strength through improved muscle contraction quality or neuromuscular function rather than direct muscle size increases [8].

3.3. Muscle Lipid Metabolism

Choline is critical for proper lipid metabolism in skeletal muscle. Decreased choline availability impairs the Kennedy pathway for PC synthesis, disrupting triacylglycerol (TAG) and fatty acid (FA) metabolism in muscle [9,10,11].

Animal studies showed choline — through increased PC synthesis — causes increased membrane lipid content (PC and sphingomyelin), reduced TAG content by ~40% and free fatty acids by ~60%, decreased lipogenesis and long-chain fatty acid biosynthesis, increased β-oxidation of fatty acids in mitochondria (energy), and reduced intramuscular fat accumulation [9,10].

In humans, choline supplementation improved body composition through decreased body fat and increased lean mass, particularly in overweight individuals. These effects suggest choline supports muscle lipid metabolism through enhanced mitochondrial efficiency and reduced chronic inflammation associated with lipotoxicity [9].

3.4. Muscle Injury and Recovery

Choline deficiency is associated with increased muscle susceptibility to mechanical injury and reduced recovery capacity [5,6,7]. Studies showed animals on choline-deficient diets exhibited elevated plasma creatine kinase (muscle damage marker) both at rest and after exercise [5,6].

Mechanisms of impaired recovery capacity in choline deficiency include: (1) muscle membrane integrity impairment where reduced PC weakens muscle membranes, increasing susceptibility to exercise-induced damage and recovery delays; (2) reduced protein synthesis where decreased methionine availability reduces protein translation and synthesis of recovery proteins essential for muscle repair; (3) decreased energy production where mitochondrial dysfunction from abnormal PC reduces ATP production capacity needed for muscle restoration [5,6].

Research confirms adequate choline intake supports faster muscle recovery post-exercise and reduces muscle damage markers [5,6,7].

4. Choline and Cardiac Health and Function

4.1. Homocysteine Control and Cardiovascular Health

Homocysteine, a sulfur-containing amino acid, is recognized as an independent, potentially modifiable cardiovascular disease risk factor [12,13,14]. Elevated homocysteine levels (hyperhomocysteinemia) associate with increased risk of myocardial infarction, stroke, peripheral vascular disease, and premature death [12,13].

Choline plays a key role in homocysteine reduction through the remethylation pathway: Homocysteine + Betaine (from choline) → [BHMT enzyme] → Methionine [12,13,14].

In this pathway, betaine (choline metabolite) serves as a methyl donor converting homocysteine to methionine, directly decreasing plasma homocysteine levels. Methionine is subsequently converted to S-adenosylmethionine (SAM), a universal methyl donor supporting numerous enzymatic pathways throughout the body [12,13].

Research shows individuals with higher choline intake have significantly lower homocysteine levels, particularly those with low folate intake [12,13]. In a large prospective study of nearly 4,000 participants, those in the highest choline intake quartile showed ~28% lower homocysteine levels compared to the lowest quartile [12].

4.2. Autonomic Nervous System Function

Choline, as an acetylcholine precursor, is essential for proper parasympathetic nervous system function (vagal), which modulates heart rate and generally leads to heart rate reduction and cardiac rhythm stabilization. Inadequate choline availability decreases ACh synthesis in parasympathetic nuclei, weakening vagal tone and leading to relatively elevated sympathetic tone — a position associated with arrhythmia risk and cardiac dysfunction [15,16].

Animal studies in spontaneously hypertensive rats (SHR, hypertension model) showed choline supplementation increased plasma ACh levels, increased baroreceptor sensitivity (cardiovascular reflex sensitivity regulating blood pressure), decreased resting heart rate and systolic blood pressure, improved left ventricular ejection fraction and fractional shortening, and reduced left ventricular hypertrophy [15,16].

These effects were mediated through increased vagal tone (parasympathetic activity) and decreased sympathetic tone [15,16]. In humans, observational studies showed individuals with

higher blood choline levels demonstrated normal heart rate variability, an indicator of cardiovascular health and cardiac adaptation capacity [15].

4.3. Oxidative Stress and Inflammation in Cardiac Muscle

Choline demonstrates protective effects against oxidative stress and inflammation — two key mechanisms in cardiovascular disease [15,16,17]. In vitro and animal studies showed choline and its forms, such as cytidine-5'-diphosphocholine (citicoline), reduce reactive oxygen species (ROS) production in cardiac muscle through increased antioxidant enzyme activity (superoxide dismutase, catalase, glutathione peroxidase), increased Nrf2 (nuclear factor erythroid 2-related factor 2) and HO-1 (heme oxygenase-1) expression (key antioxidant transcription regulators), reduced lipid peroxidation, and reduced mitochondrial Ca^{2+} release and mitochondrial dysfunction [15,16,17].

Regarding inflammation, choline reduces pro-inflammatory cytokine production, including IL-6 and TNF-α, through Toll-like receptor 4 (TLR4) pathway inhibition in endothelial cells and macrophages. Simultaneously, choline increases anti-inflammatory IL-10 cytokine production, promoting immunoregulatory phenotypes [15,16,17].

4.4. Chemotherapy Cardiotoxicity Protection

Doxorubicin, a commonly used chemotherapy drug, has notorious cardiotoxic effects, often causing cardiomyopathy and heart failure. Research shows choline provides cardioprotection during doxorubicin chemotherapy through reduced ROS and oxidative stress, prevents calcium overload in cardiomyocytes, reduces cardiac fibrosis, restores cardiac function (ejection fraction, fractional shortening), reduces cardiomyocyte apoptosis, and restores plasma ACh levels and parasympathetic activity [15,17].

These effects suggest choline may have application as an adjunctive agent in reducing doxorubicin cardiotoxicity in chemotherapy patients [15,17].

5. Choline in Athletes and Muscle Performance

5.1. Endurance Performance and Prolonged Exercise

Intense, prolonged exercise decreases free blood choline levels, potentially limiting performance. Research shows exercise exceeding 2 hours at ~70% VO_2max may decrease blood choline levels by 20–40%, depending on training conditions and nutritional status [21,22]. Short exercise (<1 hour) at low/moderate intensity shows minimal choline decrease, moderate

exercise (1–2 hours) at moderate intensity shows 10–15% choline decrease, and prolonged exercise (>2 hours) at high intensity (>70% VO_2max) shows 20–40% choline decrease [21,22].

Several mechanisms explain this choline decrease: (1) increased ACh synthesis where intense muscle activity causes increased ACh synthesis at the NMJ, increasing plasma choline uptake; (2) increased PC synthesis where exercising muscles increase PC content for membrane repair, requiring increased choline availability; (3) increased betaine oxidation where betaine metabolism may increase during exercise, decreasing available choline; (4) choline loss in sweat where prolonged exercise causes significant perspiration, with potential choline loss, though this represents a minority of total loss [21,22].

5.2. Choline Supplementation and Performance

Research shows choline supplementation may improve endurance performance, particularly in athletes with normal-to-decreased choline levels during intense exercise [21,22].

In a runner study, individuals receiving 2.8 g choline citrate (1 hour before and halfway through a 20-mile running effort) showed maintained plasma choline levels (no decrease during exercise), faster race time (~2–3% improvement), and decreased fatigue sensation in the final exercise portion [21,22].

In comparison, placebo groups showed 40% choline decline and slower race times. In Ironman triathletes, krill oil supplementation (containing significant choline as phosphatidylcholine) prevented choline decrease during Ironman races (~8–16 hours of effort) [21].

However, choline supplementation appears effective primarily for athletes performing prolonged exercise, causing choline levels to fall below normal. In shorter efforts (<1–2 hours) with minimal choline decrease, supplementation showed no significant performance effect [21,22].

5.3. Choline and Resistance Training

Studies in older adults (50–69 years) suggest choline affects resistance training strength adaptation capacity [8]. Those with low choline intake (~51% AI) demonstrated significantly smaller strength gains following 12-week resistance training compared to those consuming higher amounts (~68–118% AI) [8].

Notably, strength improvement in low-choline individuals derived mainly from improved neuromuscular function and signal transmission — not necessarily greater muscle hypertrophy

[8]. This suggests choline supports neuromuscular communication optimization and force generation capacity, rather than direct muscle size increases.

6. Dietary Choline Sources and Adequate Intake

6.1. Recommended Choline Intake

Adequate Intake (AI) for choline, established by the Institute of Medicine, is presented in the following table [18,20]:

Age Group	Males	Females	Pregnancy	Lactation
Infants (0–6 m)	125 mg/day	125 mg/day	—	—
Infants (7–12 m)	150 mg/day	150 mg/day	—	—
Children (1–3 y)	200 mg/day	200 mg/day	—	—
Children (4–8 y)	250 mg/day	250 mg/day	—	—
Children (9–13 y)	375 mg/day	375 mg/day	—	—
Adolescents (14–18 y)	550 mg/day	400 mg/day	450 mg/day	550 mg/day
Adults (≥19 y)	550 mg/day	425 mg/day	450 mg/day	550 mg/day

Table 1: Adequate Intake (AI) for Choline by Age and Sex

The Tolerable Upper Intake Level (UL) for adults is 3,500 mg/day [18,20].

6.2. Animal Product Sources

Animal products provide richer choline sources [18,19,20]:

Product	Serving	Choline (mg)	% AI*
Beef liver	100 g	418	76%
Chicken liver	100 g	290	53%

Eggs (whole, cooked)	1 large (50 g)	147	27%
Salmon	100 g	86	16%
Chicken breast	100 g	58	11%
Beef	100 g	76	14%
Cheddar cheese	28 g	24	4%
Whole milk	240 mL	38	7%

Table 2: Animal Product Sources of Choline (*Based on AI 550 mg for males)

6.3. Plant-Based Sources

Plant products contain less choline but provide important sources for vegetarians [18,19]:

Product	**Serving**	**Choline (mg)**	**% AI***
Roasted soy	1 cup (93 g)	214	39%
Edamame	1 cup (155 g)	107	20%
Tofu	150 g	90	16%
Wheat germ	84 g	153	28%
Cooked broccoli	160 g	30	5%
Cooked cauliflower	160 g	72	13%
Brussels sprouts	160 g	31	6%
Pinto beans	185 g	43	8%
Green peas	160 g	21	4%

Table 3: Plant-Based Sources of Choline (*Based on AI 550 mg for males)

7. Safety and Adverse Effects

7.1. Tolerance and Safety

Choline is generally well-tolerated when consumed in amounts near recommended intake. However, exceeding the Upper Limit (UL = 3,500 mg/day) may cause adverse effects [18,20].

Adverse effects from excessive choline intake (typically >3,000 mg/day) include: (1) fish odor (trimethylaminuria) where choline metabolism by gut bacteria creates trimethylamine (TMA), converted by the liver to trimethylamine oxide (TMAO); (2) gastrointestinal disturbance where high-dose choline supplements may cause nausea, vomiting, diarrhea, and stomach upset; (3) potential cardiovascular risk (TMAO) where some research suggests very high TMAO from choline metabolism may associate with increased cardiovascular disease risk in predisposed individuals, though primarily from excessive intake far exceeding AIs; (4) low blood pressure where very high doses (>4 g/day) may cause hypotension, dizziness, and fainting; (5) headaches where some experience headaches at high doses [18,20].

7.2. Special Populations

Pregnancy and lactation: Increased choline requirements (450 mg/day pregnancy, 550 mg/day lactation) should be easily met through a diverse diet. Supplementation should be discussed with healthcare providers [18].

Liver disease: Choline is critical for liver function, but excessive doses may stress already-compromised livers [18].

Betaine metabolism disorders: Those with rare betaine metabolism or choline transport disorders may need supplementation caution [18].

8. Practical Recommendations

8.1. Athletes

Endurance athletes: Ensure minimum 550 mg choline daily (males) or 425 mg (females) through a diverse diet; for exercise >2 hours at high intensity, consider ~2–3 g choline supplementation (choline citrate or citicoline) 1 hour pre-exercise; avoid relying exclusively on supplementation—prioritize whole-food sources; monitor choline intake through nutrition labels [21,22].

Strength/resistance athletes: Ensure 550 mg daily choline (males) through eggs, meat, poultry, fish, and cruciferous vegetables; adequate choline supports better strength adaptations during

resistance training; incorporate choline sources throughout daily meals for consistent availability [8].

8.2. Cardiovascular Health

Those with CVD risk or established disease: Ensure 425–550 mg daily choline through diverse diet including meat, poultry, fish, eggs, and cruciferous vegetables; for elevated homocysteine (>15 μmol/L), consult cardiologist about choline, folate, and B12 interactions; avoid very high choline doses (>3,000 mg/day) that may elevate TMAO; if taking other homocysteine-metabolism supplements (folate, B6, B12), read labels to avoid excessive intake [12,13,14,15,16].

8.3. Special Populations

Older adults (>65 years): Choline supports neuromuscular function and strength maintenance with age; ensure minimum adequate intake (550 mg males, 425 mg females); choline transporter activity may decrease with age, so prioritize dietary sources [8].

Endurance athletes (marathons, triathlons, Ironman): Monitor choline status through fatigue sensation in final exercise stages; if experiencing late-race fatigue, consider choline supplementation; maximum choline supplementation should not exceed 3 g/day [21,22].

9. Discussion

This narrative review synthesizes contemporary evidence demonstrating that choline plays vital roles in skeletal muscle and cardiac function through multiple interconnected biochemical pathways. Choline deficiency disrupts neuromuscular transmission, compromises muscle membrane integrity, impairs protein synthesis, and increases cardiovascular disease risk through elevated homocysteine and reduced parasympathetic function [1,3,4,6,7,8].

In skeletal muscle, choline supports neuromuscular transmission as acetylcholine precursor essential for muscle contraction initiation [1,3,4]. Chronic choline deficiency compromises muscle membrane integrity through decreased phosphatidylcholine synthesis, increasing exercise-induced muscle damage [9,10,11]. Resistance-trained adults with low choline intake demonstrate substantially reduced strength adaptation compared to those with adequate intake, with this deficit deriving from impaired neuromuscular function rather than reduced muscle hypertrophy [8]. Choline's role in muscle protein synthesis, mediated through betaine and S-adenosylmethionine availability, significantly impacts muscle growth [2,5,6]. Additionally, choline promotes fatty acid β-oxidation and reduces intramuscular triglyceride accumulation by approximately 40%, improving mitochondrial efficiency and body composition [9,10].

In cardiac health, choline reduces homocysteine levels through betaine's role in the BHMT enzyme pathway, converting homocysteine to methionine [12,13,14]. Population studies demonstrate that individuals in the highest choline intake quartile exhibit approximately 28% lower plasma homocysteine levels compared to the lowest quartile [12]. Choline's role as acetylcholine precursor supports parasympathetic nervous system function, strengthening vagal tone and promoting heart rate reduction and blood pressure control [15,16]. Animal studies demonstrate that choline supplementation improves left ventricular function through enhanced vagal tone [15,16]. Additionally, choline reduces reactive oxygen species production through increased antioxidant enzyme activity and reduces pro-inflammatory cytokine production (IL-6, TNF-α) while increasing anti-inflammatory IL-10 cytokine production [15,16,17]. Emerging evidence demonstrates choline's cardioprotective effects against chemotherapy-induced cardiotoxicity through reduced oxidative stress and prevention of calcium overload [15,17].

For athletic performance, endurance athletes performing exercise exceeding 2 hours experience substantial blood choline depletion (20-40%) and may benefit from choline supplementation (2-3 g pre-exercise) [21,22]. Resistance-trained athletes benefit most from ensuring adequate dietary choline intake (550 mg/day for men) through whole-food sources [8].

Average United States choline intake is approximately 313 mg/day, substantially below the Adequate Intake of 550 mg/day for men and 425 mg/day for women [2,20]. This gap is particularly concerning in vulnerable populations including older adults, vegetarians, athletes performing intense endurance exercise, and individuals with cardiovascular disease [2,18,20].

Several limitations warrant acknowledgment: this review integrates preclinical mechanistic studies, observational epidemiological studies, and limited human intervention trials, with human intervention trials remaining limited for most choline-related outcomes [1,2,21,22]. Most cardiovascular and muscle performance data derive from observational studies, which cannot establish causation and remain susceptible to confounding [8,12,13]. Dose-response relationships and long-term safety data remain limited [12,13,21,22].

Critical research priorities include large prospective human intervention trials examining choline supplementation effects on cardiovascular outcomes and athletic performance, genomic and microbiota investigations characterizing how genetic polymorphisms modify choline requirements, mechanistic studies in human models examining neuromuscular junction function and cardiac autonomic function, and comprehensive dose-response and safety studies [1,2,8,12,13,15,21,22]. Clinicians managing athletes, cardiovascular disease patients, and aging individuals should incorporate explicit choline assessment into nutritional evaluation. Simple dietary counseling emphasizing choline-rich whole foods (eggs, meat, poultry, fish, legumes,

cruciferous vegetables) could substantially improve population choline status with minimal cost or risk [8,18,20].

10. Conclusion

Choline represents an essential micronutrient whose importance for muscle and cardiac health has been substantially underappreciated. The convergence of mechanistic studies, observational epidemiology, and emerging intervention trials establishes clear roles in neuromuscular transmission, cardiac autonomic regulation, homocysteine control, oxidative stress reduction, and exercise performance. The widespread gap between population choline intake and physiological requirements suggests that choline insufficiency may substantially contribute to muscle dysfunction and cardiovascular disease. Current recommendations emphasizing adequate dietary choline intake (425-550 mg/day through diverse whole foods, with potential supplementation in specific contexts such as prolonged endurance exercise) represent prudent, evidence-based guidance for promoting both muscle and cardiac health across diverse populations.

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Author Contributions:

- **Conceptualization:** [TK], [MP]
- **Methodology:** [MP], [AB]
- **Software:** [TK], [AB], [MS]
- **Check:** [PR], [MP], [MS]
- **Formal analysis:** [AB], [TK]
- **Data curation:** [MP], [PR]
- **Writing-rough preparation:** [TK], [MP], [AB], [PR], [MS]
- **Writing-review and editing:** [TK], [MS]
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