Review Article

Micronutrients crosstalk with skeletal muscle during exercise: A review of synergistic interactions

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Abstract

Skeletal muscle is a highly plastic organ that undergoes significant metabolic and structural stress during exercise, necessitating precise nutritional support for adaptation and recovery. While the roles of macronutrients are well-established, the complex interplay, or "crosstalk," between essential micronutrients is a critical yet dynamic facet of exercise physiology. This review synthesizes current evidence on the synergistic relationships between key vitamins and minerals—specifically vitamin D, calcium, magnesium, the B-vitamins, antioxidants, and iron—in supporting skeletal muscle function during and after exercise. We explore how these micronutrients co-operate in energy production, calcium handling, contraction coupling, antioxidant defense, and anabolic signaling. Recent research continues to elucidate the molecular mechanisms behind this crosstalk, highlighting the role of the gut-muscle axis and the impact of deficiencies on adaptive outcomes. Understanding this intricate network is paramount for developing targeted nutritional strategies that optimize athletic performance, enhance recovery, and support long-term musculoskeletal health.

Key Words: Micronutrients, Skeletal muscle, Exercise, Synergistic effect, Antioxidants

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Introduction

Exercise induces a multitude of physiological responses in skeletal muscle, including increased energy demand, mechanical strain, oxidative stress, and inflammatory signaling (Hawley et al., 2014). The muscle's ability to adapt to these stresses—leading to improved strength, endurance, and metabolic health—is governed by intricate molecular pathways. Nutritional support is a fundamental modulator of this adaptive response.

Traditionally, micronutrients have been studied in isolation, leading to a siloed understanding of their functions. However, in the biological milieu, these nutrients exist in a dynamic network of interactions where the status of one directly influences the absorption, function, and requirement of another—a concept known as micronutrient crosstalk (Volpe, 2013). Emerging evidence up to 2024 continues to refine our understanding of these interactions, particularly within the context of exercise. This review aims to elucidate these critical interactions, focusing on their collective impact on skeletal muscle during exercise, and integrates the most recent findings in the field.

1. The calcium-magnesium-vitamin D triad in excitation-contraction coupling

The process of muscle contraction is initiated by an action potential leading to the release of calcium (Ca^{2+}) from the sarcoplasmic reticulum. This fundamental process relies on a delicate balance between several minerals.

• Calcium (Ca^{2+}) and Magnesium (Mg): Mg^{2+} remains recognized as a natural calcium antagonist, essential for stabilizing excitable membranes and facilitating muscle relaxation (Nielsen & Lukaski, 2006). Newer research confirms that Mg deficiency exacerbates exercise-induced oxidative stress and inflammatory responses, further impairing muscle function and recovery (Zhang et al., 2022). The efficiency of the SERCA pump, crucial for re-sequestering Ca^{2+}, is highly dependent on Mg-ATP.

Table 1. Micronutrient crosstalk in skeletal muscle during exercise.

Micronutrient Pair/Group	Primary Individual Functions	Synergistic Crosstalk During Exercise	Supporting References (Including Recent Studies)
Vitamin D, Calcium (Ca^{2+}), Magnesium (Mg)	Vit D: Regulates gene expression for Ca^{2+} handling and mitochondrial proteins. Ca^{2+}: Primary signal for muscle contraction. Mg: Cofactor for ATPases; natural Ca^{2+} channel blocker.	Vitamin D ensures adequate Ca^{2+} availability and supports mitochondrial function. Ca^{2+} influx initiates contraction. Mg facilitates relaxation (SERCA pump), provides energy (ATP), and modulates oxidative stress.	(Ceglia & Harris, 2013; Nielsen & Lukaski, 2006; Zhang et al., 2022; Chang et al., 2024; Oshima et al., 2023)
B-Vitamins (B1, B2, B3, B5, B6, B7, B9, B12)	Act as essential coenzymes in carbohydrate, fat, and protein metabolism (e.g., TCA cycle, ETC, glycogenolysis).	Function as an interdependent enzymatic team. Gut microbiota may contribute to the production of certain B-vitamins (B2, B7, B9, B12), creating a gut-muscle axis that influences availability.	(Woolf & Manore, 2006; Kern et al., 2023; Ticinesi et al., 2024)
Antioxidants: Vit E, Vit C, Se, & Polyphenols	Vit E: Protects cell membranes. Vit C: Scavenges radicals in plasma. Se: Cofactor for GPx. Polyphenols: Modulate antioxidant pathways.	Vitamin C regenerates oxidized Vitamin E. GPx enzymes (Se) reduce peroxides. Polyphenols (e.g., curcumin) may potentiate the effects of classic antioxidants, enhancing recovery from damage.	(Traber & Stevens, 2011; Ristow et al., 2009; Psaraki et al., 2022; Tanabe et al., 2023)
Iron, Vitamin C, B2 (Riboflavin)	Iron: Core component of hemoglobin and myoglobin. Vit C: Enhances non-heme iron absorption. B2: Supports iron metabolism.	Vitamin C increases non-heme iron absorption and may attenuate the exercise-induced rise in hepcidin, improving iron availability. Riboflavin status influences iron mobilization.	(Woolf & Manore, 2006; Koehler et al., 2022; Dzik et al., 2023)

• Vitamin D: The vitamin D receptor (VDR) is expressed in muscle tissue and regulates the transcription of genes involved in calcium handling (Ceglia & Harris, 2013). Recent longitudinal studies have strengthened the link between vitamin D sufficiency and improved muscle strength and power output, particularly in athletes with initially insufficient levels (Oshima et al., 2023). Furthermore, a 2024 mechanistic study demonstrated that vitamin D directly influences mitochondrial function in skeletal muscle, suggesting a broader role beyond calcium homeostasis in supporting aerobic capacity and fatigue resistance (Chang et al., 2024).

This triad demonstrates clear crosstalk: Vitamin D supports calcium availability and mitochondrial health, calcium initiates contraction, and magnesium facilitates relaxation and modulates oxidative stress. An imbalance in any one can disrupt the entire contraction-relaxation cycle and adaptive response.

2. B-Vitamin synergy in energy metabolism and the gut-muscle axis

The B-complex vitamins function primarily as coenzymes in energy metabolic pathways. Their functional interdependence is well-established, but recent research has expanded into novel areas.

• Energy Metabolism: The role of B-vitamins (B1, B2, B3, B5, B6, B7, B9, B12) as an interdependent enzymatic team in the citric acid cycle, electron transport chain, and amino acid metabolism remains foundational (Woolf & Manore, 2006). A 2023 review emphasized that high-intensity exercise may increase the turnover and loss of certain B-vitamins (e.g., B2 and B6), thereby elevating dietary requirements to prevent a metabolic bottleneck that limits ATP production (Kern et al., 2023).

• The Gut-Muscle Axis: A novel area of research involves the crosstalk between gut microbiota, B-vitamin production, and muscle function. Certain gut bacteria are producers of B-vitamins, including B2, B7, B9, and B12. A 2024 hypothesis paper proposed that exercise-induced shifts in the gut microbiome could influence local and systemic availability of these microbial-derived vitamins, potentially impacting muscle protein synthesis and recovery (Ticinesi et al., 2024). This suggests a complex, indirect crosstalk where gut health influences micronutrient status and, consequently, muscle physiology.

3. Antioxidant defense: selenium, vitamin e, vitamin c, and polyphenols

The management of exercise-induced oxidative stress involves a sophisticated network of enzymatic and non-enzymatic antioxidants.

• The Classic Synergy: The cooperation where vitamin C regenerates oxidized vitamin E, and selenium-dependent glutathione peroxidases (GPx) reduce peroxides, remains a core principle (Traber & Stevens, 2011). The caution against high-dose isolated antioxidant supplementation, which can blunt adaptive hermetic responses (Ristow et al., 2009), has been reinforced by recent meta-analyses showing that such practices may interfere with mitochondrial biogenesis and endurance training adaptations (Psaraki et al., 2022).

• New Players and Interactions: Recent studies have explored interactions with dietary polyphenols. For example, research in 2023 showed that combining vitamin C with curcumin enhanced the recovery of muscle strength and reduced markers of muscle damage after eccentric exercise more effectively than either compound alone, suggesting a potentiation of antioxidant and anti-inflammatory effects (Tanabe et al., 2023). This indicates

that the antioxidant crosstalk network is even more extensive than previously thought, involving phytonutrients.

4. Iron, vitamin C, and the oxygen delivery system

Iron's role in oxygen transport and utilization is paramount for athletic performance, and its interaction with other nutrients is critical.

• Iron and Vitamin C: The enhancing effect of vitamin C on non-heme iron absorption is well-documented. A 2022 randomized controlled trial demonstrated that co-ingesting 100 mg of vitamin C with a plant-based meal significantly improved iron status biomarkers in female athletes with low ferritin over a 12-week period (Koehler et al., 2022).

• Beyond Absorption: New evidence suggests that vitamin C may also play a role in mitigating exercise-induced hepcidin elevation. Hepcidin is a hormone that blocks iron absorption and recycling. Strenuous exercise increases hepcidin levels, potentially impairing iron availability for hours afterwards. A 2023 study found that vitamin C supplementation prior to exercise attenuated the post-exercise hepcidin response, suggesting a novel mechanism by which vitamin C supports iron metabolism in athletes (Dzik et al., 2023).

Conclusion

The evidence clearly indicates that micronutrients function not as isolated entities but as an integrated network within the exercising skeletal muscle. Recent research up to 2024 has deepened our understanding of this crosstalk, revealing new molecular mechanisms (e.g., vitamin D on mitochondria), novel interactions (e.g., with polyphenols), and even systemic pathways like the gut-muscle axis (As illustrated in Figure 1).

The cellular drama of muscle contraction is orchestrated by precise ionic shifts, where micronutrients act as essential co-directors. The fundamental mechanism of excitation-contraction coupling is governed by the flux of calcium (Ca^{2+}). An action potential triggers the release of Ca^{2+} from the sarcoplasmic reticulum (SR) through ryanodine receptors (RyR1), flooding the cytosol and allowing Ca^{2+} to bind troponin C, which initiates the cross-bridge cycling of actin and myosin filaments. The critical crosstalk begins with magnesium (Mg^{2+}), which acts as a natural calcium antagonist by competing for binding sites on RyR1, stabilizing the channel and preventing excessive leakage, thereby fine-tuning the force of contraction. For muscle relaxation, Ca^{2+} must be rapidly pumped back into the SR via the

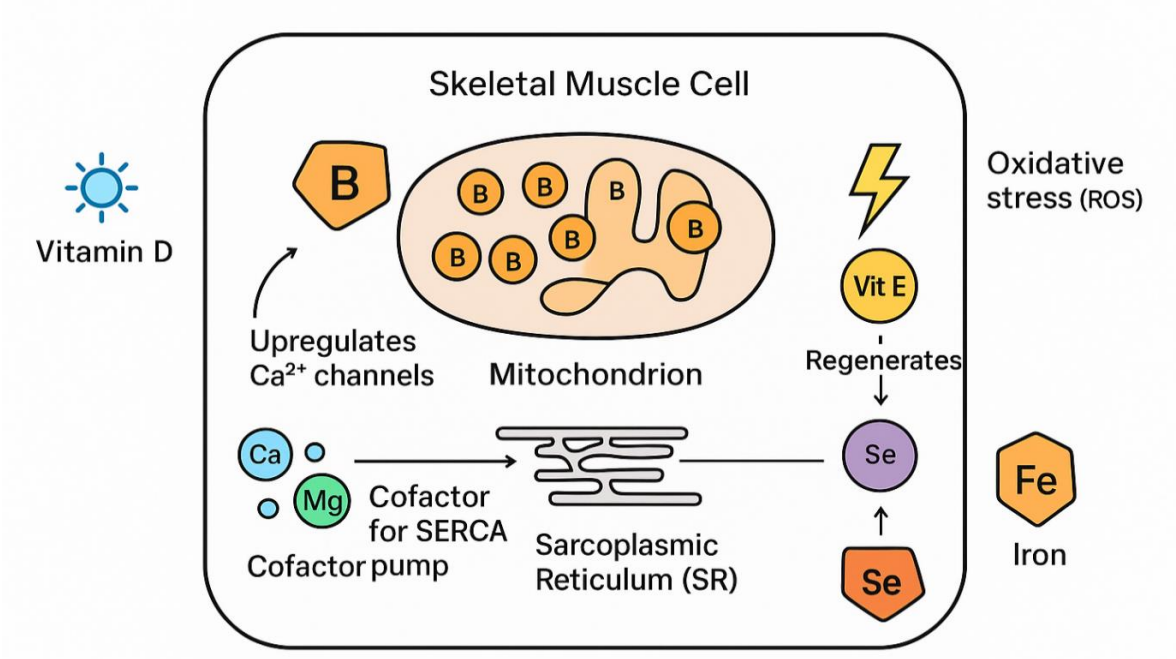

Figure 1. Schematic representation of key micronutrient crosstalk networks within skeletal muscle during exercise. The illustration highlights four primary interactive systems: (1) The Calcium-Magnesium-Vitamin D triad regulates excitation-contraction coupling at the sarcoplasmic reticulum (SR); Vitamin D upregulates calcium channels, Ca^{2+} release initiates contraction, and Mg^{2+} acts as a Ca^{2+} antagonist and essential cofactor for the SERCA pump responsible for relaxation. (2) B-Vitamins act as synergistic coenzymes driving energy production (TCA cycle, electron transport chain) within the mitochondrion. (3) The Antioxidant network (Vitamins C, E, Selenium) functions cooperatively to mitigate exercise-induced oxidative stress; Vitamin C regenerates oxidized Vitamin E, while Selenium is a core component of the glutathione peroxidase (GPx) enzyme. (4) Iron's absorption and metabolism are facilitated by Vitamin C (which enhances non-heme iron uptake and may attenuate hepcidin) and Vitamin B2. Arrows denote facilitatory interactions; blunted lines indicate inhibition.

SERCA pump, an ATP-dependent process for which Mg^{2+} is an indispensable cofactor as a component of Mg-ATP. Vitamin D enters this mechanism not as a passive spectator but as a genomic regulator. The binding of active 1,25-dihydroxyvitamin D to the vitamin D receptor (VDR) in the muscle cell nucleus modulates the expression of genes encoding key proteins like RyR1 and those involved in calcium influx across the membrane, thereby influencing the very infrastructure of calcium handling (Ceglia & Harris, 2013). A deficiency in any component of this triad—D, Mg, or Ca—disrupts this delicate balance, leading to impaired contractile force, prolonged relaxation, and muscle fatigue.

Beyond mechanical function, micronutrient crosstalk is vital for managing the metabolic and oxidative consequences of exercise. Within the mitochondrion, B-vitamins function as indispensable coenzymes in a concerted biochemical symphony. For instance, the decarboxylation reactions of the pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes in the TCA cycle are utterly dependent on thiamine (B1), while riboflavin (B2) is the precursor for FAD and FMN, critical for accepting and donating electrons in the electron transport chain (ETC). A deficiency in a single B-vitamin creates a metabolic bottleneck, halting ATP production and increasing the diversion of metabolites into alternative pathways, ultimately compromising endurance. This heightened metabolic flux inevitably increases the generation of reactive oxygen species (ROS) from the ETC. Here, a second tier of molecular crosstalk is activated for redox homeostasis. Selenium is incorporated into the active site of glutathione peroxidases (GPx), enzymes that catalytically reduce hydrogen peroxide and lipid hydroperoxides to water and harmless alcohols. In the lipid-rich environment of the cellular membrane, vitamin E (α-tocopherol) neutralizes lipid peroxyl radicals, becoming oxidized in the process. This oxidized vitamin E is then regenerated back to its active reduced state by vitamin C (ascorbate) in the aqueous cytosol, a quintessential example of nutrient recycling (Traber & Stevens, 2011). This cooperative defense system ensures that ROS serve as important signaling molecules for adaptation (e.g., via Nrf2 pathway activation) without causing detrimental oxidative damage to proteins, lipids, and DNA that would impair recovery and function.

Future research must continue to adopt a multi-nutrient, systems-based approach. Human trials investigating combined micronutrient supplementation, reflecting their synergistic roles and based on individual athlete genotype and microbiome profile, are needed. Furthermore, the impact of different exercise modalities on micronutrient requirements and interactions warrants further exploration. For practitioners and athletes, the emphasis remains on promoting a diverse, whole-food, nutrient-dense diet that provides a full spectrum of vitamins, minerals, and phytonutrients, thereby supporting the natural and efficient crosstalk that underpins optimal muscle function and adaptation to exercise.

What is already known on this subject?

Traditionally, micronutrients have been studied in isolation, leading to a siloed understanding of their functions. However, in the biological milieu, these nutrients exist in a dynamic network of interactions where the status of one directly influences the absorption, function, and requirement of another—a concept known as micronutrient crosstalk.

What this study adds?

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Data availability

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Compliance with ethical standards

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