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Micronutrients in Metabolic Syndrome: A Comprehensive Review

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ABSTRACT

Metabolic syndrome (MetS) represents a cluster of interconnected risk factors for cardiovascular disease and type 2 diabetes mellitus. This review1 examines the emerging evidence on the role of micronutrients in the pathophysiology, prevention, and management of MetS. Recent research has highlighted significant associations between micronutrient status and the components of MetS, including insulin resistance, dyslipidemia, hypertension, and central obesity. This review synthesizes findings from studies published between 2015 and 2025, focusing on vitamins (D, B complex, E, C), minerals (magnesium, chromium, zinc, selenium), and other bioactive compounds. Current evidence suggests that micronutrient deficiencies may contribute to the development and progression of MetS, while targeted supplementation strategies show promise as adjunctive therapeutic approaches. We discuss potential mechanisms of action, clinical implications, and future research directions to elucidate the complex interplay between micronutrient status and metabolic health.

Keywords

Metabolic syndrome, Micronutrients, Vitamins, Minerals, Insulin resistance, Supplementation.

Introduction

Metabolic syndrome (MetS) is a complex clinical entity characterized by the co-occurrence of multiple interconnected metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension. The global prevalence of MetS continues to rise, with estimates suggesting that approximately 25-30% of adults worldwide are affected, presenting a significant public health challenge [1]. This alarming increase is largely attributed to the adoption of sedentary lifestyles and unhealthy dietary patterns characteristic of modern societies.

While macronutrient imbalances have received considerable attention in MetS research, the role of micronutrients has emerged as an area of growing interest over the past decade. Micronutrients, including vitamins and minerals, serve as essential cofactors in numerous metabolic pathways and cellular processes that regulate glucose homeostasis, lipid metabolism, blood pressure, and inflammatory responses [2]. Mounting evidence suggests that micronutrient deficiencies may contribute to the pathophysiology of MetS and its components, while optimal micronutrient status may confer protective effects against metabolic dysfunction.

This review aims to synthesize the current understanding of the relationship between micronutrients and MetS, examining evidence from observational studies, clinical trials, and mechanistic investigations published between 2015 and 2025. We explore the roles of key vitamins, minerals, and other bioactive compounds in metabolic health, discussing potential mechanisms of action and clinical implications for prevention and management strategies.

Methodology

This review followed a systematic approach to identify relevant literature published between January 2015 and April 2025. Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched using combinations of terms related to metabolic syndrome (e.g., "metabolic syndrome," "insulin resistance," "dyslipidemia," "hypertension," "central obesity") and micronutrients (e.g., "micronutrient," "vitamin," "mineral," "trace element," with specific nutrient names). Studies were included if they: (1) were

published in English; (2) examined the relationship between one or more micronutrients and MetS or its components; and (3) involved human subjects or relevant experimental models. Priority was given to randomized controlled trials, systematic reviews, meta-analyses, and large prospective cohort studies.

Vitamins and Metabolic Syndrome

Vitamin D

Vitamin D deficiency has been consistently associated with increased risk of MetS and its individual components. A meta-analysis of 18 observational studies involving 99,745 participants demonstrated that individuals with vitamin D deficiency (<20 ng/mL) had a 52% higher risk of MetS compared to those with sufficient levels [3]. Similarly, data from the National Health and Nutrition Examination Survey (NHANES) 2011-2018 revealed an inverse relationship between serum 25-hydroxyvitamin D concentrations and the prevalence of MetS, with each 10 ng/mL increase in vitamin D levels associated with 24% lower odds of MetS.

The beneficial effects of vitamin D on metabolic health may be mediated through several mechanisms. Vitamin D receptors are expressed in pancreatic β-cells, adipocytes, and skeletal muscle, suggesting direct modulatory effects on glucose metabolism. Recent evidence indicates that vitamin D enhances insulin sensitivity by promoting insulin receptor expression and glucose transporter 4 (GLUT4) translocation [4]. Additionally, vitamin D's anti-inflammatory properties may attenuate the chronic low-grade inflammation characteristic of MetS.

Intervention studies examining vitamin D supplementation in MetS have yielded mixed results. A meta-analysis of 23 randomized controlled trials (RCTs) involving 1,503 participants with MetS reported that vitamin D supplementation significantly improved insulin sensitivity and reduced fasting blood glucose levels, particularly at doses exceeding 4,000 IU/day and among individuals with baseline vitamin D deficiency [5]. However, another systematic review concluded that vitamin D supplementation had minimal effects on blood pressure and lipid profiles in MetS patients.

Recent studies have highlighted the potential for personalized approaches to vitamin D supplementation. Thota et al. conducted a randomized controlled trial among 240 individuals with MetS and found that a genotype-guided vitamin D supplementation strategy targeting individuals with specific vitamin D receptor polymorphisms resulted in greater improvements in metabolic parameters compared to a standardized supplementation protocol.

B Vitamins

The B-vitamin complex plays crucial roles in energy metabolism, homocysteine metabolism, and mitochondrial function, all of which have implications for metabolic health. Accumulating evidence suggests associations between B-vitamin status and MetS components.

Folate (Vitamin B9)

Folate deficiency has been linked to insulin resistance and endothelial dysfunction. A cross-sectional study involving 1,530 adults found that serum folate levels were inversely associated with HOMA-IR (homeostatic model assessment for insulin resistance) scores and MetS prevalence [6]. Mechanistically, folate contributes to the regulation of homocysteine levels, with hyperhomocysteinemia being a recognized risk factor for cardiovascular complications in MetS.

Intervention studies suggest potential benefits of folate supplementation in MetS. A 12-week RCT in 120 MetS patients demonstrated that daily supplementation with 5 mg folate significantly improved endothelial function, reduced inflammatory markers, and enhanced insulin sensitivity compared to placebo. Similarly, Setola et al. reported that combined supplementation with folate and vitamin B12 reduced homocysteine levels and improved flow-mediated dilation in individuals with MetS and hyperhomocysteinemia.

Vitamins B6 and B12

Vitamins B6 and B12, along with folate, are involved in one-carbon metabolism and homocysteine regulation. Low levels of these vitamins have been associated with increased cardiometabolic risk. A prospective cohort study following 1,670 adults over 7 years found that lower baseline plasma vitamin B6 levels predicted the development of MetS, independent of traditional risk factors.

Intervention studies focusing specifically on vitamins B6 and B12 in MetS are limited. However, a recent factorial design RCT involving 240 individuals with prediabetes and MetS reported that combined supplementation with vitamins B6, B12, and folate for 24 weeks resulted in significant improvements in insulin sensitivity and β-cell function compared to placebo, while individual vitamin supplements showed more modest effects [7].

Vitamin E

Vitamin E, a potent lipid-soluble antioxidant, may protect against oxidative stress-induced metabolic dysfunction. Observational studies have reported inverse associations between vitamin E status and MetS prevalence. Analysis of the NHANES 2011-2016 data revealed that serum α-tocopherol levels below 20 μmol/L were associated with 1.8-fold higher odds of MetS after adjusting for confounders.

Experimental studies have elucidated several mechanisms by which vitamin E may influence metabolic health. Vitamin E enhances insulin sensitivity through activation of insulin receptor substrate (IRS) and phosphoinositide 3-kinase (PI3K) signaling pathways in skeletal muscle and adipose tissue. Furthermore, vitamin E protects pancreatic β-cells against oxidative damage and improves mitochondrial function [8].

Clinical trials investigating vitamin E supplementation in MetS have shown promising results. A double-blind RCT involving 86 patients with MetS demonstrated that daily supplementation with

400 IU of vitamin E for 6 months significantly reduced oxidative stress markers, improved insulin sensitivity, and decreased high-sensitivity C-reactive protein levels compared to placebo [9]. Similarly, Tabrizi et al. reported that vitamin E supplementation (800 IU/day for 12 weeks) improved endothelial function and reduced systolic blood pressure in individuals with MetS.

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble antioxidant with potential benefits for metabolic health. A meta-analysis of 15 observational studies found an inverse association between vitamin C status and MetS risk, with a 24% lower prevalence of MetS among individuals in the highest quantile of vitamin C intake or serum concentration compared to those in the lowest quantile.

Recent mechanistic studies suggest that vitamin C may enhance glucose uptake in skeletal muscle through increased GLUT4 expression and translocation [10]. Additionally, vitamin C improves endothelial function by increasing nitric oxide bioavailability and reducing oxidative stress [11].

Intervention studies examining vitamin C supplementation in MetS have yielded mixed results. A systematic review and meta-analysis of 8 RCTs involving 332 participants with MetS concluded that vitamin C supplementation (500-1000 mg/day) modestly improved fasting glucose levels and blood pressure but had no significant effects on lipid profiles or waist circumference [12]. However, a recent placebo-controlled trial among 164 individuals with MetS found that high-dose vitamin C supplementation (2000 mg/day for 16 weeks) significantly improved endothelial function, reduced inflammation, and enhanced insulin sensitivity, particularly in those with baseline vitamin C insufficiency [13].

Minerals and Metabolic Syndrome

Magnesium

Magnesium is an essential cofactor for over 300 enzymatic reactions, including those involved in glucose metabolism and insulin signaling. Epidemiological studies consistently demonstrate an inverse relationship between magnesium intake or status and MetS risk. A meta-analysis of prospective cohort studies involving 31,876 participants found that higher magnesium intake was associated with a 17% lower risk of MetS development over a median follow-up of 7.6 years.

Mechanistically, magnesium influences insulin sensitivity through multiple pathways. Magnesium is a cofactor for tyrosine kinase activity at insulin receptors and regulates calcium homeostasis, which affects insulin secretion and action [14]. Additionally, magnesium deficiency promotes systemic inflammation and oxidative stress, both of which contribute to metabolic dysfunction.

Clinical trials have demonstrated beneficial effects of magnesium supplementation on metabolic parameters. A meta-analysis of 21 RCTs involving 1,362 individuals with MetS or insulin resistance reported that magnesium supplementation significantly improved fasting glucose, HOMA-IR, triglycerides, and high-density lipoprotein cholesterol levels. More recently, a double-blind RCT in 120 individuals with MetS found that magnesium supplementation (400 mg/day as magnesium citrate for 24 weeks) significantly reduced blood pressure and improved markers of endothelial function compared to placebo.

Emerging evidence suggests that the form of magnesium supplementation may influence efficacy. Organic magnesium salts (e.g., magnesium citrate, magnesium lactate) appear to have superior bioavailability compared to inorganic forms (e.g., magnesium oxide), potentially leading to greater metabolic benefits [15].

Chromium

Chromium is an essential trace element involved in carbohydrate and lipid metabolism. Experimental studies indicate that chromium enhances insulin action by promoting glucose uptake in insulin-sensitive tissues through augmentation of insulin receptor signaling and GLUT4 translocation.

Observational studies examining the relationship between chromium status and MetS are limited due to difficulties in measuring chromium status accurately. However, several intervention studies have evaluated the effects of chromium supplementation on metabolic parameters. A systematic review and meta-analysis of 28 RCTs concluded that chromium supplementation (typically as chromium picolinate, 200-1000 μg/day) modestly improved glycemic control in individuals with type 2 diabetes or glucose intolerance, with more pronounced effects observed among those with poor baseline glycemic control [16].

Specific to MetS, a double-blind RCT in 96 individuals with MetS reported that chromium supplementation (400 μg/day as chromium picolinate for 16 weeks) significantly improved insulin sensitivity and reduced visceral adiposity compared to placebo. Similarly, Liu et al. [17] found that chromium-enriched yeast supplementation (400 μg/day for 12 weeks) improved lipid profiles and reduced inflammatory markers in MetS patients.

Zinc

Zinc is involved in numerous aspects of cellular metabolism and plays critical roles in insulin synthesis, storage, and secretion. A meta-analysis of observational studies revealed that individuals with MetS had significantly lower serum zinc concentrations compared to healthy controls, with a standardized mean difference of -0.45 (95% CI: -0.67 to -0.23) [6].

Mechanistic studies have demonstrated that zinc influences insulin signaling through several pathways. Zinc ions inhibit protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling, thereby enhancing insulin receptor phosphorylation and downstream signaling [18]. Additionally, zinc possesses antioxidant properties and modulates adipocyte function and adipokine secretion.

Clinical trials examining zinc supplementation in MetS have

shown promising results. A recent meta-analysis of 12 RCTs involving 678 participants with MetS or its components concluded that zinc supplementation significantly improved glycemic control, reduced triglyceride levels, and increased high-density lipoprotein cholesterol concentrations [19]. More specifically, a double-blind RCT in 60 women with MetS found that zinc supplementation (30 mg/day as zinc gluconate for 12 weeks) significantly reduced insulin resistance, inflammatory markers, and oxidative stress compared to placebo [20].

Selenium

Selenium is an essential trace element and a constituent of selenoproteins, which have important antioxidant functions. The relationship between selenium status and MetS appears to be U-shaped, with both deficiency and excess potentially contributing to metabolic dysfunction.

Observational studies have reported conflicting findings regarding selenium status and MetS risk. A cross-sectional analysis of NHANES data (2011-2016) found a positive association between serum selenium concentrations and MetS prevalence among U.S. adults, particularly at levels exceeding 150 µg/L. In contrast, a prospective cohort study in a selenium-deficient Chinese population demonstrated that lower baseline selenium status was associated with increased risk of developing MetS over a 6-year follow-up period.

Mechanistically, selenium influences glucose metabolism and insulin signaling through selenoproteins, particularly glutathione peroxidases and selenoprotein P. Optimal selenium levels appear to protect against oxidative stress and inflammation, while excessive selenium intake may induce insulin resistance through various mechanisms, including interference with insulin signaling pathways.

Intervention studies examining selenium supplementation in MetS are limited and show mixed results. A double-blind RCT in 70 individuals with MetS from a selenium-deficient region found that selenium supplementation (200 µg/day as selenium-enriched yeast for 24 weeks) improved insulin sensitivity and reduced oxidative stress markers compared to placebo. However, another RCT conducted in a selenium-replete population reported no beneficial effects of selenium supplementation on metabolic parameters, and possibly adverse effects on glucose metabolism.

Other Bioactive Compounds

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant that plays a crucial role in mitochondrial electron transport and energy production. Observational studies have reported lower plasma CoQ10 levels in individuals with MetS compared to healthy controls. Additionally, plasma CoQ10 concentrations have been inversely associated with markers of oxidative stress and inflammation in MetS patients.

Clinical trials have demonstrated beneficial effects of CoQ10 supplementation on various components of MetS. A meta-analysis of 14 RCTs involving 693 participants concluded that CoQ10 supplementation significantly reduced systolic blood pressure by 4.8 mmHg and diastolic blood pressure by 3.1 mmHg on average, with more pronounced effects observed at higher doses (≥100 mg/day). Another systematic review and meta-analysis found that CoQ10 supplementation improved glycemic control and reduced insulin resistance in individuals with metabolic disorders.

Specific to MetS, a double-blind RCT in 80 individuals with MetS reported that CoQ10 supplementation (200 mg/day for 12 weeks) significantly improved endothelial function, reduced oxidative stress markers, and enhanced antioxidant capacity compared to placebo. Similarly, Zahedi et al. demonstrated that CoQ10 supplementation (100 mg/day for 8 weeks) improved lipid profiles and reduced inflammatory markers in MetS patients.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a potent antioxidant and cofactor for mitochondrial enzymes involved in energy metabolism. Experimental studies suggest that ALA enhances insulin sensitivity through multiple mechanisms, including activation of insulin signaling pathways, modulation of AMPK activity, and reduction of oxidative stress and inflammation.

Clinical trials have demonstrated beneficial effects of ALA supplementation on metabolic parameters. A meta-analysis of 24 RCTs involving 1,316 participants concluded that ALA supplementation significantly improved lipid profiles, reduced fasting blood glucose levels, and decreased HOMA-IR scores compared to placebo [21]. More recently, a double-blind RCT in 90 individuals with MetS found that ALA supplementation (600 mg/day for 16 weeks) significantly improved insulin sensitivity, reduced waist circumference, and enhanced antioxidant status compared to placebo [22].

Interestingly, emerging evidence suggests potential synergistic effects when ALA is combined with other micronutrients. A factorial design RCT involving 120 individuals with MetS demonstrated that combined supplementation with ALA (600 mg/day) and magnesium (400 mg/day) for 12 weeks resulted in greater improvements in insulin sensitivity and endothelial function compared to either supplement alone.

Micronutrient Interactions and Combined Supplementation Approaches

While individual micronutrients have been extensively studied in the context of MetS, growing evidence suggests that micronutrient interactions and combined supplementation approaches may offer enhanced benefits for metabolic health. Several mechanisms underlie these interactions, including synergistic antioxidant activities, complementary effects on insulin signaling pathways, and mutual influences on bioavailability and metabolism.

A systematic review of 18 RCTs examining multimicronutrient supplementation in MetS concluded that combined interventions

generally yielded greater improvements in metabolic parameters compared to single-nutrient approaches. For instance, a double-blind RCT in 130 individuals with MetS demonstrated that a comprehensive micronutrient supplement containing therapeutic doses of vitamins D, E, and C, along with magnesium, zinc, and chromium, resulted in significant improvements in insulin sensitivity, lipid profiles, and blood pressure compared to placebo over a 24-week intervention period.

Recent research has also explored targeted combinations based on mechanistic interactions. A factorial design RCT in 160 individuals with MetS found that combined supplementation with vitamin D (4000 IU/day) and magnesium (400 mg/day) for 16 weeks resulted in greater improvements in insulin sensitivity and β-cell function compared to either supplement alone, suggesting synergistic effects on glucose metabolism [23]. Similarly, Fernandez-Lazaro et al. [24] reported that combined supplementation with zinc (30 mg/day) and vitamin C (1000 mg/day) for 12 weeks enhanced antioxidant capacity and reduced inflammatory markers to a greater extent than individual supplements in MetS patients.

The concept of personalized micronutrient supplementation based on individual baseline status and genetic factors is gaining traction. A recent precision nutrition trial involving 280 individuals with MetS utilized baseline micronutrient status, genetic profiles, and metabolic parameters to design personalized supplementation protocols. After 36 weeks, the personalized approach resulted in significantly greater improvements in MetS components compared to a standardized multimicronutrient supplement [25].

Clinical Implications and Future Directions

The evidence reviewed herein suggests that micronutrient status plays a significant role in the pathophysiology and management of MetS. Several clinical implications emerge from these findings:

1. Routine assessment of micronutrient status: Given the prevalence of micronutrient deficiencies and their associations with metabolic dysfunction, routine assessment of key micronutrients (particularly vitamin D, magnesium, and zinc) may be warranted in individuals with or at risk for MetS.
2. Targeted supplementation strategies: Rather than universal supplementation approaches, current evidence supports targeted supplementation based on documented deficiencies. This personalized approach may maximize benefits while minimizing potential risks associated with excessive intake of certain micronutrients.
3. Integration with lifestyle interventions: Micronutrient optimization should be considered as an adjunctive strategy alongside established lifestyle interventions for MetS, including caloric restriction, physical activity, and dietary pattern modifications.
4. Consideration of drug-nutrient interactions: Healthcare providers should be aware of potential interactions between commonly prescribed medications for MetS components (e.g., statins, antihypertensives, metformin) and micronutrient status or supplementation.

Future research directions in this field should address several knowledge gaps:

1. Long-term trials: Most intervention studies to date have been relatively short (≤24 weeks). Longer-term trials are needed to evaluate the sustainability of benefits and potential adverse effects of micronutrient supplementation in MetS.
2. Optimal dosing and combinations: Further research should elucidate optimal dosing regimens and identify the most effective micronutrient combinations for specific MetS phenotypes.
3. Precision nutrition approaches: Studies incorporating genetic, metabolomic, and microbiome analyses may help identify subgroups of MetS patients most likely to benefit from specific micronutrient interventions.
4. Mechanisms of action: More detailed mechanistic studies are needed to fully understand how micronutrients influence the complex pathophysiology of MetS and its components.
5. Cost-effectiveness analyses: Economic evaluations should assess the cost-effectiveness of micronutrient interventions relative to other management strategies for MetS.

Conclusion

This comprehensive review highlights the important role of micronutrients in the development, prevention, and management of MetS. Accumulating evidence suggests that optimal status of several vitamins (particularly D, B complex, E, C) and minerals (magnesium, chromium, zinc) may confer protection against metabolic dysfunction through various mechanisms, including enhanced insulin sensitivity, reduced oxidative stress and inflammation, and improved endothelial function. Targeted supplementation strategies based on individual micronutrient status appear promising as adjunctive approaches to established lifestyle interventions for MetS. Future research should focus on elucidating optimal dosing regimens, identifying effective micronutrient combinations, and developing personalized approaches based on genetic factors and baseline micronutrient status. Such efforts may contribute to more comprehensive and effective strategies for addressing the growing global burden of MetS and its complications.

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