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VITAMIN B12 IN ENERGY METABOLISM AND ITS ASSOCIATION WITH BODY WEIGHT

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Abstract: *Vitamin B12 (cobalamin) is an important water-soluble micronutrient that serves as one of the key inputs for cellular metabolism, especially DNA synthesis, methylation, and mitochondrial function. Its function spreads to fundamental energy production pathways by serving predominantly as a co-factor with two important mammalian enzymes such as methionine synthase (MTR) and methylmalonyl-CoA mutase (MMUT). The MMUT-catalyzed reaction bridges catabolism of certain amino acids and odd-chain fatty acids to the tricarboxylic acid (TCA) cycle, a cellular energy production-evolving center. The MTR reaction is essential for the methionine cycle and global methylation during nucleotide synthesis. These essential functions have led to heightened interest in the association of vitamin B12 in metabolic health and, as such, body weight control. Serum B12 levels consistently have an inverse association with body mass index (BMI), with lower reported levels reported in individuals with obesity. It remains uncertain, though, whether low levels of B12 in the body promote weight gain or if obesity-related factors lead to lower B12 levels. This review summarizes the biochemical status of vitamin B12, discuss its unique roles within energy metabolism, and review the evidence from human studies relating B12 status and body weight. We assess possible mechanisms of action like lipid metabolism, insulin resistance, or mitochondrial performance, but we emphasize that research to date is limited and B12 itself should not be regarded as an actual weight-losing agent. Grasping this nuanced interplay will be particularly important for students of the biochemistry and the medicine disciplines who wish to link micro-nutrient status with metabolic health on a systemic level.*

Key words: *Vitamin B12; energy metabolism; mitochondrial function; body weight; obesity; methylmalonyl-CoA.*

INTRODUCTION

Vitamin B12 is a structurally complex organometallic compound that humans must obtain from the diet, primarily from animal-derived foods. Classical vitamin B12 deficiency results in severe hematological and neurological disorders, such as megaloblastic anemia

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and myeloneuropathy. Beyond these well-established clinical manifestations, increasing attention has been directed toward the metabolic consequences of subclinical vitamin B12 deficiency, particularly in the context of the global obesity epidemic.

Obesity, characterized by excess adiposity, is a major risk factor for metabolic disorders including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. While obesity is primarily driven by an imbalance between energy intake and expenditure, micronutrients are increasingly recognized as potential modulators of metabolic efficiency and substrate utilization. Vitamin B12 occupies a central biochemical position in intermediary metabolism, acting as an essential cofactor for only two mammalian enzymes: methionine synthase and L-methylmalonyl-CoA mutase. Through these enzymes, vitamin B12 participates in one-carbon metabolism and the catabolism of propionyl-CoA, processes that are directly linked to mitochondrial function, energy production, and epigenetic regulation.

A growing body of observational studies has reported an inverse association between circulating vitamin B12 concentrations and body mass index across different populations. However, these findings do not establish causality and raise the question of whether altered vitamin B12 status contributes to metabolic dysregulation or represents a secondary consequence of obesity-related changes. This narrative review aims to provide an evidence-based overview of vitamin B12 biochemistry, its role in energy metabolism, and the current human evidence linking vitamin B12 status with body weight, while maintaining a critical perspective that avoids portraying vitamin B12 as a direct weight-loss factor

Absorption, Transport, and Intracellular Processing of Vitamin B12

Vitamin B12 absorption is a complicated, multistep process that involves a host of binding proteins and receptors that must all work together. Dietary B12 (initially bound to food proteins) is released in the stomach by gastric acid and pepsin. Free B12 is then bound to the protein haptocorrin (R-protein), which preserves and protects free B12 from acidic breakdown and degradation. In the duodenum, pancreatic proteases degrade haptocorrin, allowing vitamin B12 to associate with intrinsic factor, a glycoprotein secreted by gastric parietal cells.

The intrinsic factor–vitamin B12 complex remains digestion-resistant and is absorbed in the terminal ileum by receptor-mediated endocytosis of the cubilin–amnionless complex. After absorption, vitamin B12 then enters circulation bound with transport proteins above mentioned, especially haptocorrin and transcobalamin. Although most circulating B12 is bound to haptocorrin, the transcobalamin–B12 complex

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(holotranscobalamin) represents the biologically active fraction responsible for tissue delivery via specific transcobalamin receptors.

After cellular uptake, holotranscobalamin is internalized by receptor-mediated endocytosis and processed in lysosomes, where transcobalamin is degraded and free vitamin B12 is released into the cytosol. Vitamin B12 is then enzymatically converted into its two active coenzyme forms: methylcobalamin and adenosylcobalamin. Methylcobalamin acts as a cytosol cofactor with methionine synthase; adenosylcobalamin is produced by mitochondria and is a cofactor with methylmalonyl-CoA mutase. However, this intracellular compartmentalization further reveals vitamin B12's dual function as a cytosolic one-carbon metabolism and mitochondrial energy-producing pathway. Disruption of any phase of absorption, transport, or intracellular processing can lead to functional vitamin B12 deficiency, even when diets are adequate.

Vitamin B12-Dependent Pathways in Energy Metabolism

Pathway	**Enzyme**	**B12 Co-factor**	**Cellular locaation**	**Metabolic role & Consequences of Deficiency**
Methionine Cycle / One-carbon Metabolism	Methionine Synthase (MTR)	Methylcobalamin (MeCbL)	Cytosol	Regenerates methionine from homocysteine and tetrahydrofolate from 5-MTHF. Links folate and methionine metabolism. Deficiency leads to elevated homocysteine, impaired DNA synthesis (megaloblastic anemia), and disrupted methylation reactions.
Catabolism of Odd-Chain Fatty Acids & Certain Amino Acids	Methylmaalonyl-CoA Mutase (MMUT)	Adenosilcobalamin (AdoCbl)	Mitochondria	Converts L-methylmalonyl-CoA to succinyl-CoA, an intermediate of the TCA cycle. Provides an anaplerotic entry point into central energy Deficiency leads to accumulation of methylmalonic acid (MMA), impaired energy production from these substrates, and potential mitochondrial dysfunction.

Mitochondrial Function, Metabolic Efficiency, and Body Weight Regulation.

Mitochondria represent the main sites at which cells convert energy and are key to metabolic homeostasis. Vitamin B12 plays a role in mitochondrial metabolism as a

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cofactor for methylmalonyl-CoA mutase, an enzyme responsible for linking the catabolism of odd-chain fatty acids and specific amino acids to the tricarboxylic acid (TCA) cycle. Abnormal methylmalonyl-CoA mutase activity in vitamin B12 deficiency can cause a variety of mitochondrial-relevant changes via interconnected mechanisms that are involved in energy balance. A failure to convert methylmalonyl-CoA to succinyl-CoA is considered a metabolic bottleneck constraining anaplerotic input to the TCA cycle and consequently, potentially compromising ATP efficiency and substrate utilization.

Moreover, upstream metabolites like methylmalonic acid and propionyl-CoA have been accumulated by experimental models and have affected mitochondrial respiration, promoted oxidative stress, and affected electron transport chain activity. In addition to its canonical cofactor status, vitamin B12 may have antioxidant properties within mitochondria, scavenging reactive oxygen species such as superoxide as well as maintaining intracellular glutathione concentrations. Oxidative stress may be a major factor to mitochondrial dysfunction and is a strong motivator of obesity-related insulin resistance.

Vitamin B12 deficiency may, thus, worsen mitochondrial oxidative damage, which in turn impairs mitochondrial metabolic homeostasis and fuel oxidation. Moreover, diminished levels of S-adenosylmethionine due to impaired methionine synthase activity may act as a catalyst for epigenetic control of lipids and glucose metabolizing genes. These mechanisms, when considered in combination, offer biological plausibility for association of vitamin B12 status and metabolic health, but would not support direct causal role of vitamin B12 in body weight regulation.

Association between Vitamin B12 Status and Body Weight: Evidence from Human Studies.

Epidemiological studies have consistently reported an inverse relationship between circulating vitamin B12 concentrations and measures of adiposity, including body mass index (BMI) and waist circumference. Cross-sectional analyses in children, adolescents, and adults indicate that individuals with higher BMI or obesity tend to have lower serum B12 levels. For example, Aureli et al. (2023) observed a linear decrease in serum B12 across a cohort of over 600 children and young adults, with lower B12 associated not only with higher BMI and waist circumference but also with markers of hepatic insulin resistance and steatosis. Similar patterns have been reported in adult populations, with meta-analyses confirming significantly lower B12 concentrations in obese versus non-obese individuals

Several mechanisms have been proposed to explain this association, although causality remains unestablished. First, B12 deficiency may contribute to metabolic inefficiency, altered lipid metabolism, and fatigue, potentially promoting positive energy balance. Second, obesity itself may reduce B12 status via chronic low-grade inflammation, altered transcobalamin metabolism, hemodilution of water-soluble vitamins, or dietary

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patterns low in B12-rich foods. Third, confounding factors such as socioeconomic status, physical activity, and overall diet quality may influence both vitamin B12 status and body weight.

Importantly, intervention studies do not support a direct role of vitamin B12 supplementation in weight reduction among non-deficient individuals. While correcting deficiency can alleviate fatigue or other symptoms, B12 administration has not been shown to reliably induce weight loss in the general population or in those with obesity. Observed associations are therefore more likely to reflect correlative or secondary effects rather than a causal influence of B12 on body weight.

Vitamin B12 Deficiency and Indirect Metabolic Consequences relevant to Body Weight

Beyond its direct role in the TCA cycle, B12 deficiency may indirectly influence body weight through its effects on other metabolic processes.

Altered Lipid Metabolism: Pre-clinical and clinical studies suggest a link between low B12 status and dyslipidemia. Animal models have shown that maternal B12 deficiency can lead to offspring with excess fat accumulation, higher insulin resistance, and an adverse lipid profile. In humans, B12 deficiency has been associated with increased lipogenesis and reduced lipolysis, potentially promoting an atherogenic lipid profile and fat storage. The mechanisms may involve altered methylation of genes controlling lipid metabolism or disruption of fatty acid oxidation in mitochondria.

Insulin Resistance: Insulin resistance is a hallmark of obesity and a precursor to type 2 diabetes. Several studies have reported an association between low B12 levels and increased insulin resistance, even in non-diabetic individuals. The connection may be mediated by elevated homocysteine, which can induce endoplasmic reticulum stress and impair insulin signaling, or by B12's role in mitochondrial function and oxidative stress management.

Fatigue and Reduced Energy Expenditure: One of the most common and debilitating symptoms of clinical and subclinical B12 deficiency is fatigue and weakness. This can lead to a reduction in spontaneous physical activity and overall energy expenditure. Over time, this decrease in the "energy out" side of the energy balance equation could contribute to gradual weight gain or hinder weight loss efforts.

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