



Research Paper

## Correlation between Vitamin B12 Status and Insulin Resistance: A Review

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Running title: Vitamin B12 and Insulin Resistance

### Abstract

Insulin resistance (IR) is a central feature of type 2 diabetes mellitus (T2DM), metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), and adverse cardiometabolic outcomes. Vitamin B12 (cobalamin) is essential for one-carbon metabolism and mitochondrial function; deficiency remains common, particularly with dietary restriction, malabsorption, or prolonged metformin exposure. Observational studies often report that lower circulating vitamin B12 is associated with higher surrogate indices of IR (fasting insulin and HOMA-IR), although null and context-dependent findings also occur. Mechanistic hypotheses include impaired methyl-group availability, hyperhomocysteinemia, oxidative stress, endothelial dysfunction, adipose inflammation, and altered lipid handling. Interventional evidence is limited and heterogeneous; selected trials suggest that B12 (often combined with folate) may improve glycemic indices and IR in metabolically high-risk groups, but causality remains uncertain due to confounding and reverse causation—especially where metformin use is common. This review summarizes key epidemiologic and mechanistic evidence and proposes priorities for future trials using robust insulin sensitivity outcomes and functional B12 biomarkers.

**Keywords:** Vitamin B12; cobalamin; insulin resistance; HOMA-IR; metabolic syndrome; metformin; homocysteine; NAFLD; PCOS.

### I. Introduction

Insulin resistance is defined by reduced tissue responsiveness to insulin signaling, resulting in compensatory hyperinsulinemia and metabolic abnormalities. Micronutrient status may influence insulin sensitivity through effects on mitochondrial energetics, redox balance, and methylation-dependent gene regulation. Vitamin B12 is a cofactor for methionine synthase and methylmalonyl-CoA mutase, linking one-carbon metabolism with mitochondrial substrate handling.

Vitamin B12 deficiency occurs due to low intake of animal-source foods, malabsorption syndromes, and drug effects. Metformin is consistently associated with lower B12 levels and biochemical deficiency, particularly with longer duration and higher dose.<sup>1,2</sup>

### Epidemiologic Evidence

In population-based cohorts, lower B12 status frequently clusters with higher adiposity and more adverse metabolic profiles. In a prospective cohort of US adults, higher dietary intake and serum concentrations of B vitamins, including B12, were inversely associated with incident metabolic syndrome.<sup>3</sup>

A meta-analysis reported an inverse association between vitamin B12 levels and metabolic syndrome, while homocysteine demonstrated a positive association, supporting a link between disrupted one-carbon metabolism and metabolic risk.<sup>4</sup>

### Pregnancy and PCOS

A meta-analysis examining vitamin B12 and gestational diabetes mellitus found lower B12 was associated with GDM in multiple studies and emphasized the potential importance of folate:B12 balance; some cohorts also reported higher HOMA-IR among women with lower B12.<sup>5</sup>

In PCOS, lower plasma B12 has been reported in association with greater obesity and insulin resistance.<sup>6</sup>

Conversely, Mendelian randomization evidence did not support a causal relationship between genetically predicted B12 and PCOS risk, indicating likely confounding in observational studies.<sup>7</sup>

### Interventional Evidence

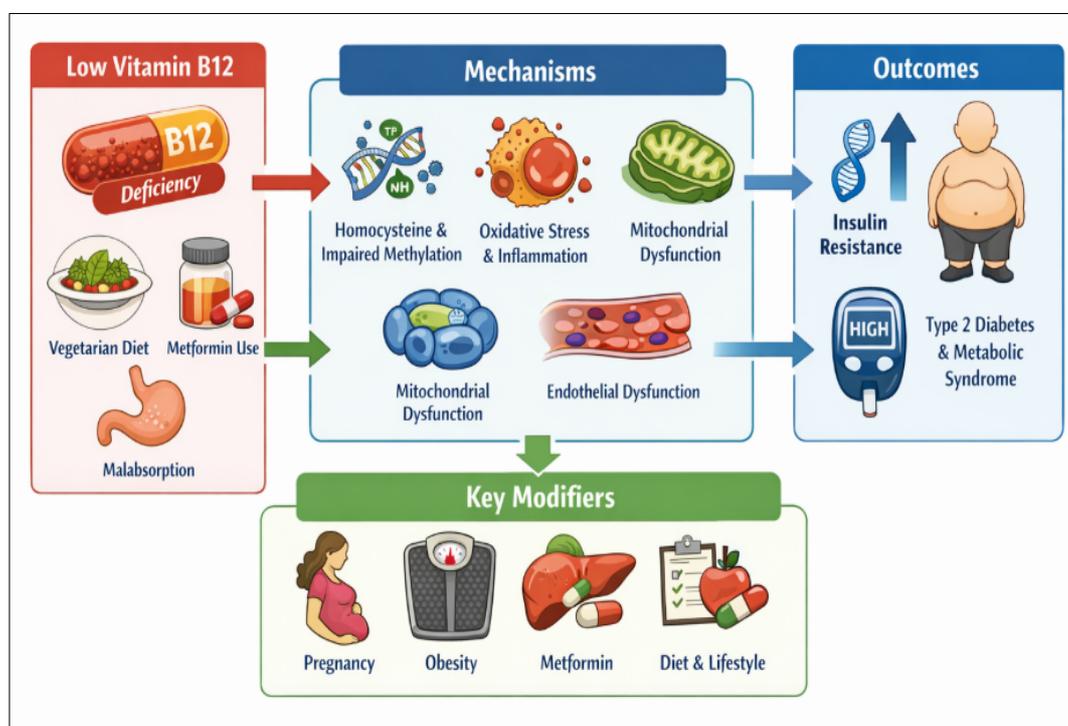
In T2DM, add-on supplementation with vitamin B12 (with folic acid) improved glycemic control and insulin resistance indices compared with control conditions.<sup>8</sup>

In NAFLD, a double-blind placebo-controlled trial of oral vitamin B12 (1,000 micrograms/day for 12 weeks) reduced homocysteine and reported changes in metabolic and liver-related markers.<sup>9</sup>

### Mechanistic Links

Low B12 can reduce methyl-group availability and increase homocysteine, which may promote oxidative stress, impair nitric oxide bioavailability, and contribute to endothelial dysfunction—features associated with insulin resistance.<sup>4</sup>

Functional B12 deficiency (elevated methylmalonic acid) may impair mitochondrial substrate flux and lipid oxidation. Metformin is both a confounder and potential effect modifier; analyses should account for dose and duration, and trials should stratify by metformin exposure.



**Fig 1: Vitamin B12, One-Carbon Metabolism, and Insulin Resistance: Mechanistic Overview**

### Clinical Implications and Research Priorities

B12 assessment is most justified in groups at high risk of deficiency, especially individuals receiving long-term metformin. Where serum B12 is borderline, functional biomarkers may better reflect tissue-level insufficiency. Treating confirmed deficiency is standard of care; recommending B12 solely to improve insulin sensitivity in non-deficient individuals is not currently evidence-based.<sup>1,2</sup>

Future randomized trials should stratify by baseline deficiency and metformin exposure, use standardized biomarker panels, and include robust insulin sensitivity outcomes.

## II. Conclusion

Lower vitamin B12 status is frequently associated with insulin-resistant phenotypes, but causality remains uncertain. Mechanistic pathways are plausible, and limited trial data suggest potential benefit of B12-containing regimens in selected high-risk populations. Deficiency-stratified randomized trials are required to determine whether correcting B12 insufficiency can meaningfully improve insulin resistance beyond established neurologic and hematologic benefits.

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