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Vitamin B12 and diabetic peripheral neuropathy: something old and something new to make the relationship stronger

Aims: To describe novel data about intrinsic antioxidative activity of vitamin B12 (B12) that may provide a rationale for its use in treating diabetic peripheral neuropathy (DPN), even in early subclinical states.
Methods: The authors dealt with the chemical aspects and causes of B12 deficiency and focused on the pathophysiological involvement of B12 in the development of DPN (as a cofactor and as a redox system). Then the clinical and the biochemical parameters of overt or subclinical B12 deficiency are described, by differentiating more sensitive biomarkers and cut-offs, for both general and elderly population.
Results: The important role of B12 deficiency in DPN is supported by several studies. In particular, reduced B12 bioavailability may lead to reduced methylmalonyl-CoA mutase activity and subsequently elevated methylmalonyl acid (MMA) levels may cause extensive mitochondrial dysfunction and elevated radical oxygen species (ROS) production. In addition to its function as a cofactor, B12 works as a redox system thanks to its central Cobalt atom. In this way, B12 protects against superoxide-induced nerves injury at several stages: (1) by scavenging ROS, (2) by preserving high glutathione levels, (3) by reducing oxidative stress caused by metabolic pathways, and (4) by modulating cytokine production. For this impact on nerves, B12 deficiency should be rule out, also in absence of overt clinical symptoms and signs. Four laboratory parameters are available: serum total B12, Holotranscobalamin (HoloTC), homocysteine (HCys), and methylmalonic acid (MMA). No one of these parameters could represent alone the lack of B12, but they could be used together to refine the diagnosis. In particular, HoloTC levels react earlier and appear more sensitive for documenting B12 deficiency while HCys and MMA are influenced by renal function, especially in elderly patients. An algorithm for the detection of B12 deficiency, adapted and modified from Herrmann W and Obeid R (*Dtsch Arztebl Int. 2008;10:680-5*.) is also proposed.
Conclusions: The recognition of intrinsic antioxidative activity of B12 indicates a new role of this molecule in DPN pathophysiology, beyond its classical cofactor function. Because of this additional reason, B12 supplementation could be justified to treat and even to prevent the development of DPN.
Comment. This well-structured and complete review investigates most aspects of the relationship between B12 and DPN. B12 deficiency is common in people with diabetes and in elderly (possibly related to reduced kidney function or drugs such as proton-pump inhibitors or metformin). Because of its link with DPN, this aspect should be screened and monitored, even in absence of overt signs or symptoms, more than we do in everyday clinical practice. However, nowadays no single biomarker is able to represent all possible aspects of B12 deficiency (screening, subclinical deficiency, overt deficiency) and cut-off values for each biomarker and each phase need to be defined (and more attention should be deserved to elderly people). Moreover, in literature there is no univocal evidence about the beneficial effect of B12 supplementation on DPN. Further studies are needed to clarify the antioxidative action of B12 administration, particularly in the early stages of DPN.

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Reference. Schleicher E, Didangelos T, Kotzakioulafi E, Cegan A, Peter A, Kantartzis K. Clinical Pathobiochemistry of Vitamin B12 Deficiency: Improving Our Understanding by Exploring Novel Mechanisms with a Focus on Diabetic Neuropathy. Nutrients. 2023 Jun 1;15(11):2597. doi: 10.3390/nu15112597. PMID: 37299560; PMCID: PMC10255445.
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