VITB12 DEFICIENCY IN METFORMIN USERS AND RELATION TO RENAL FUNCTIONS IN TYPE2DM

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Abstract:
Vitamin B12 deficiency is common among patients with type 2 diabetes mellitus (T2D). Although metformin therapy is the principal factor , advanced age with types DM,nutritional deficiency,and malabsorption are other contributing factors ***(1)***
The proposed mechanisms for deficiency include impairment of calcium-dependent absorption from the gut, alteration in small bowel motility resulting in bacterial overgrowth, and a reduction in intrinsic factor levels ***(2).***Several studies have reported that metformin-induced vitamin B12 deficiency contributes to the high prevalence and/or worsening of existing peripheral neuropathy in patients with T2D ***(3).***

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Introduction

Vitamin B12 deficiency is common among patients with type 2 diabetes mellitus (T2D). Although metformin therapy is the principal factor , advanced age with types DM,nutritional deficiency,and malabsorption are other contributing factors ***(1)***
The proposed mechanisms for deficiency include impairment of calcium-dependent absorption from the gut, alteration in small bowel motility resulting in bacterial overgrowth, and a reduction in intrinsic factor levels ***(2).***Several studies have reported that metformin-induced vitamin B12 deficiency contributes to the high prevalence and/or worsening of existing peripheral neuropathy in patients with T2D ***(3).***
Several studies have investigated the individual effects of dose and duration of metformin therapy on vitamin B12 levels. The reported results are inconsistent with some studies reporting an association with the dose but not the duration ***(4)*** and other studies reporting an association only for the duration ***5)*** .A few studies did not find an association with either the dose or the duration ***(6)*** and low prevalence of vitamin B12 deficiency

Physiological roles of vitamin B12

Vitamin B12 exerts its physiological effects through mediating two principal enzymatic pathways i.e. the methylation process of homocysteine to methionine and the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA. Vitamin B12 as a co-factor facilitates the methylation of homocysteine to methionine which is later activated into S-adenosyl-methionine that donates its methyl group to methyl acceptors such as myelin, neurotransmitters and membrane phospholipids.(7)
Metabolically significant vitamin B12 deficiency hence will result in disruption of the methylation process and accumulation of intracellular and serum homocysteine. Hyperhomocysteinemia has been shown to have potentially toxic effects on neurones and the vascular endothelium. This reaction is also essential in the conversion of dietary folate (methyl-tetrahydrofolate) to its active metabolic form, tetrahydrofolate. In another essential enzymatic pathway, vitamin B12 as a co-factor mediates the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA. In the presence of vitamin B12 deficiency, this conversion pathway is diminished and an increase in the serum methylmalonic acid (MMA) ensues. This is followed by defective fatty acid synthesis of the neuronal membranes [3]. Vitamin B12 is also essential in the synthesis of monoamines or neurotransmitters like serotonin and dopamine [4]. This synthesis is impaired with vitamin B12 deficiency.
All the above collectively explain the resultant neuro-cognitive or psychiatric manifestations that accompany vitamin B12 deficiency. Axonal demyelination, degeneration and later death are the hallmark of vitamin B12 deficiency induced neuronal damage that manifests as severe peripheral or autonomic neuropathy, sub acute combined degeneration of the spinal cord, delirium and dementia [3,5]. Compelling evidence demonstrates that hyperhomocysteinemia is also associated with an increased risk of cardiovascular events due to its cellular and vasculo-toxic effects [6-8].

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