

A genetic perspective of Metformin induced Vitamin B12 deficiency in Type 2 Diabetes mellitus patients



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ABSTRACT

Metformin, a commonly prescribed hypoglycemic agent is a first line medication for the management of Type 2 diabetes mellitus. Numerous studies have depicted that metformin therapy has been associated with vitamin B12 and folate deficiency. Vitamin B12 deficiency is frequently missed or misdiagnosed by the clinicians because it is not routinely tested by most of the physicians, further the low end of the laboratory reference range is too low and misinterpreted as diabetic peripheral neuropathy. Vitamin B12 deficiency is a silent epidemic with serious consequences. Long term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B12 leading to its deficiency and neurological manifestations. Polymorphisms of certain genes associated with the metabolism of vitamin B12 and folate might help in predicting the deficiency status of vitamin B12.

Keywords: Single nucleotide polymorphism, Metformin, Vitamin B12 deficiency, Type 2 diabetes mellitus

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INTRODUCTION

Worldwide a large group of population is affected by Type 2 diabetes mellitus (T2DM). T2DM is a complex heterogeneous group of metabolic disorders which includes hyperglycemia with impaired insulin action and/or insulin secretion.¹ It is said that Metformin is considered as a cornerstone in the treatment of Diabetes and is the most frequently prescribed first line drug for type 2 Diabetes mellitus patients, which is associated with improvements in cardio vascular disease risk.² The risk of developing vitamin B12 deficiency is increased to a ratio of 2.88 with intake of 1g daily intake of the drug metformin.³ Only few studies were published regarding the genetic perspectives of metformin induced vitamin B12, folate and homocysteine deficiency.^{4,5}

METFORMIN

Monotherapy with metformin which is the favored initial drug of choice has been proved as safe and low cost with weight

neutrality, and improve cardiovascular outcomes.⁶ Metformin and lifestyle intervention reduced the incidence of diabetes by 58% and 31%, respectively, when compared with placebo.⁷ The only effective drug which lowers blood glucose concentrations in T2DM patients without causing overt hypoglycemia is metformin. Its improvement in insulin sensitivity could be due to its effects on insulin receptor expression and tyrosine kinase activity causing reduction in insulin resistance and significant reduction of plasma fasting insulin level.⁸

METFORMIN INDUCED B12 DEFICIENCY: AN INVISIBLE EPIDEMIC

Hydroxycobalamin or Cyanocobalamin, commonly called as Vitamin B12 belongs to a family of substances composed of tetrapyrrole rings surrounding a central cobalt atom with nucleotide side chains attached to the cobalt.⁹

Sixteen weeks of treatment with metformin is associated with 14% reduction in vitamin B12 concentration in T2DM

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patients.¹⁰ Vitamin B12 deficiency is indicated by anaemia and increased mean corpuscular volume (MCV).¹¹ Many studies report that metformin which is a first-line drug used in the treatment of T2DM patients reduce serum B12 levels by 10–30%.¹² The absorption of Vitamin B12 is affected by (a) alterations in intestinal motility, (b) increased bacterial overgrowth, (c) alterations of B12-IF complex. The risk of developing metformin induced B12 deficiency is increased by (a) increasing age, (b) metformin dosage, (c) duration of usage.¹³

COBALAMIN & FOLATE RELATION

An essential cofactor involved in one-carbon metabolism and responsible for biosynthesis of purine and thymidine nucleotide which is concerned with methylation reactions and epigenetic influences (DNA, chromosomes and mutations) is folate.¹⁴⁻¹⁷ Folate is associated with many reactions in mammalian tissues. Of these only two reactions require Cobalamin, isomerization and methylation of Methylmalonyl Co-A and homocysteine to methionine respectively. These two reactions require both methylcobalamin and 5MTHF. This reaction is first step in pathway by which 5MTHF, which enters bone marrow and other cells from plasma, is converted into all the intracellular folate co-enzyme.¹⁷

Manifestations in metformin induced vitamin B12 and folate deficiency

Neurological symptoms, such as paresthesia, impaired vibration sensation and proprioception, which are a potential result of neurological damage are seen in patients with metformin-induced vitamin B12 and folate deficiency. Many clinicians may falsely diagnose these symptoms as diabetic peripheral neuropathy.^{17,18}

Diagnostic tests for B12 & folate deficiency

- Serum Cobalamin
- Serum Methylmalonate and Homocysteine
- Serum folate
- Red cell folate.¹⁹⁻²²

Single nucleotide polymorphism (SNP)

DNA sequence variation occurring when a single nucleotide A, T, C, or G in the genome (or shared sequence) differs between members of a species (or between paired chromosomes in an individual) is known as Single nucleotide polymorphisms (SNP). Due to their high density and relatively even distribution in the human genomes, SNPs have emerged as genetic markers of choice. This has paved a pathway to many groups for fine mapping of the disease loci and for locating the candidate genes.²³ Recently, several studies have attributed SNPs of the genes involved

in folate metabolism and their role in related diseases.²⁴⁻²⁷ The present review depicts the SNPs involved in vitamin B12 and folate metabolic pathway.

BETAINE-HOMOCYSTEINE S METHYLTRANSFERASE (BHMT)

This enzyme participates in the metabolism of glycine, serine, threonine and also methionine. Transfer of a methyl group from trimethylglycine and a hydrogen ion from homocysteine to produce dimethylglycine and methionine respectively is catalyzed by BHMT. Thus it is important in homocysteine and 1-carbon metabolism.²⁸⁻³⁰ BHMT polymorphism is associated with hyper homocysteinemia and B12 deficiency.³¹

CHOLESTERYL ESTER TRANSFER PROTEIN (CETP)

The interchange of triglycerides from LDL and VLDL for cholesteryl esters from HDL is performed by Cholesteryl ester transfer protein, otherwise known as plasma lipid transfer protein.^{32,33} Polymorphisms in the CETP gene have been associated with the risk for diabetic complications in patients with T2DM and signifies B12 deficiency.³⁴

METHYLENE TETRAHYDROFOLATE REDUCTASE (MTHFR)

MTHFR gene codes for the rate limiting enzyme in methyl cycle, acting as a co-substrate for methylating homocysteine to methionine. It has been observed that there is a greater chance of getting vitamin B12 deficiency along with increased homocysteine levels in those people with MTHFR polymorphisms. Also vitamin B12 deficient subjects are prone for developing MTHFR polymorphisms.³⁵

METHYL TETRAHYDROFOLATE HOMOCYSTEINE METHYLTRANSFERASE (MTR)

MTR codes for the enzyme Methionine synthase which regenerates methionine from homocysteine. Vitamin B12 acts as a cofactor for this reaction wherein folic acid and B12 work synergistically. Homocysteinuria with B12 deficiency is well correlated with the polymorphisms associated with MTR gene.³⁶

FUCOSYLTRANSFERASE 2 (FUT2)

This gene belongs to a multiple gene family coding for the enzyme fucosyl transferase (FUT1–FUT7). The H

antigen which is a common precursor for the blood group antigens A and B, is synthesised in a precursor form by this enzyme fucosyl transferase coded by FUT2.³⁷ SNP in fucosyl transferase (FUT2) gene is associated with the levels of plasma vitamin B12 which might suggest some alteration in b12 absorption leading to alteration in the plasma levels.^{38,39}

TRANSCOBALAMIN II (TCN 2)

Holotranscobalamin transports vitamin B12 (around 20%) from its site of absorption in the ileum to tissues and cells. This B12 is called Active B12. The balance 80% of the circulating B12 is bound with haptocorrin, the function of which is to be elucidated.⁴⁰ Megaloblastic anemia and other manifestations of vitamin B12 deficiency results with the polymorphism of transcobalamin II.⁴¹

CONCLUSION

It is obvious that T2DM patients on higher dose and long term use of metformin are under the risk of developing Vitamin B12 and folate deficiency. This emphasizes the routine screening for their deficiency in T2DM patients under metformin therapy for more than 5 years, even in absence of hematological and neurological manifestations.

There are only a limited number of studies on SNPs of the various genes involved in Vitamin B12 and folate metabolism, especially those genes associated with B12 deficiency induced by Metformin. So a detailed analysis of these genes is vital to know which will help in predicting B12 and folate deficiency before it actually appears.

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CA – Concept of the review, manuscript preparation and critical revision of the manuscript; **RR** – Concept of the review and scrutinizing the manuscript; **GR** – Concept of the review; **ARS** – Concept of the review.

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