

Research Article

Is the Use of Metformin Associated with Vitamin B12 Deficiency in Hospitalized Patients?

Madill J*, Hartman B, Donnelly-VanderLoo, Smeall K, Siswanto O, Watson T and O'Connor C

School of Food and Nutritional Sciences, Brescia University College, London, ON, Canada

*Address for Correspondence: Janet Madill, Brescia University College, 1285 Western Road, London, Ontario, Canada, E-mail: jmadill7@uwo.ca

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ABSTRACT

Objective: The primary objective was to determine the prevalence of vitamin B₁₂ deficiency and subclinical deficiency among metformin users in various clinical settings across Southwestern Ontario. The secondary objective was to determine the relationship between metformin use and B₁₂ deficiency.

Methods: A retrospective chart review was conducted on patients admitted to emergency, neurology, critical care and trauma, and spinal cord and stroke rehabilitation units in 3 hospitals across Southwestern Ontario between January 2010 and December 2012. A total of 710 electronic charts were studied through random sampling.

Results: Overall prevalence of impaired B₁₂ status (<220 pmol/L) among the entire patient population with B₁₂ data were 18.6% (n=391) and 24% among metformin users (n=78, P < 0.0001). The majority of metformin users were not likely to take a B₁₂ supplement (P=0.0065). The 2 patients on metformin who were both classified as being B₁₂ deficient, however, only 53% of those with subclinical deficiency were taking a B₁₂ supplement. B₁₂ supplement administration did differ by hospital site in those with subclinical B₁₂ deficiency status (148-220 pmol/L, P=0.0334).

Conclusion: This study reports a higher prevalence of B₁₂ deficiency among metformin users than the general patient population. Metformin users with overt B₁₂ deficiency were taking B₁₂ supplements but only half of those with subclinical deficiency were using a B₁₂ supplement. Recommendations for B₁₂ supplement use among those with subclinical status vary by institution. Measuring methylmalonic acid [MMA] to determine functional B₁₂ status may ensure those with subclinical deficiencies receive treatment, and this should become the standard medical approach.

Keywords: Metformin, Cobalamin, Vitamin B₁₂, Deficiency, Type 2 diabetes, Neuropathy

Introduction

After the United Kingdom Prospective Diabetes Study [1], metformin has commonly been used as the first hypoglycemic agent of choice for the treatment of type 2 diabetes as it has been shown to reduce the risk of diabetes related microvascular and macrovascular complications [1]. In addition to decreasing the risk of stroke, myocardial infarction, and death [2-5], metformin has been associated with less weight gain and a decrease in hypoglycemic episodes [1-5]. Since metformin is extensively used in the diabetic population, its side effects are well documented. Numerous studies report that approximately 10-30% of patients taking metformin experience

vitamin B₁₂ (B₁₂ malabsorption [2,3,5-14]. The most current and likely method of action is through altering the calcium-dependent uptake of B₁₂ in the distal ileum [2-9,11,14-16] which is supported by the reversal of metformin-induced B₁₂ deficiency by supplemental calcium [2-4,7-9,16]. B₁₂ malabsorption can lead to B₁₂ deficiency (<148 pmol/L), which can have serious complications, including weakness [7,8,17], dementia [7,15,18], confusion [7], difficulty maintaining balance [7], and neurological changes [7,8,15,17-20]. If not adequately treated, B₁₂ deficiency can result in permanent nerve damage [7]. Symptoms of B₁₂ deficiency as also seen in those with marginal B₁₂ status (148-220 pmol/L); further, the high folate status commonly seen in folate-fortified countries has been shown to further exacerbate symptoms of an impaired B₁₂ status (<220 pmol/L) [21-23].

The absence of a standardized protocol to assess B₁₂ status during metformin therapy is problematic as B₁₂-related neuropathy may be misread as diabetic neuropathy [15,20]

The primary objective of this study was to determine the prevalence of vitamin B₁₂ deficiency among metformin users in select clinical settings across Southwestern Ontario. The secondary objective was to determine if there is an association between metformin use and B₁₂ deficiency. Administration of B₁₂ supplementation among those with a B₁₂ deficiency was also assessed to determine if these individuals are at risk of developing irreversible neurological damage.

Methods

Patients & study design

A retrospective chart review was conducted in 3 university-affiliated hospitals, including 2 acute-care hospitals and a rehabilitation and complex care hospital in Southwestern Ontario. Electronic charts of patients aged 18 and older that were admitted to emergency, neurology, critical care and trauma, and spinal cord and stroke rehabilitation units between January 1, 2010 and December 31, 2012 were examined. These settings were chosen, as they are settings where patients with neurological impairments and/or damage are more likely to present. Sample size for categorical data was calculated to ensure 10-20 events per variable (EPV) [24]. Recording data on 20 variables required a minimum of 200-400 charts to be reviewed. Through random sampling, a total of 710 charts were analyzed.

Measures

A data abstraction tool was created for this study based on measures of interest. The primary measure was B₁₂ status as measured by serum B₁₂. There is some inconsistency with regards to cut-offs for Vitamin B₁₂ deficiency, however, more recently accepted cutoffs are 148 pmol/L for deficiency and between 148-220 for marginal or subclinical deficiency status [25,26]. Secondary variables were metformin use, dose, and duration. Other variables of interest included hospitals, units of admission, sex, age, reason for admission, signs of B₁₂ deficiency (B₁₂) signs of deficiency were confirmed through having at least one symptom of either confusion, dementia, paresthesias, bizarre behaviour, fall, ataxia, and/or hallucination), RBC folate, mean corpuscular volume (MCV), hemoglobin, serum iron, albumin, B₁₂ supplementation, iron supplementation, folic acid supplementation, multivitamin/multimineral supplementation, and pernicious anemia.

Data collection & analysis

Before data collection began, 3 trained research assistants (RAs) pilot tested the data abstraction tool to ensure it was reliable. A reference manual was created to standardize data collection. Inter-rater reliability was measured as a percentage of agreement between the 3 RAs for 3 different patient charts. An inter-rater reliability score of 92% was achieved, meeting the recommendations of at least 80% for important variables [27]. Next, the RAs recorded the measures of interest from patients' electronic charts. If a patient had multiple admissions during the specified time frame, the first admission was used to record the reason for admission and lab data. Charts with missing data will be treated by the maximum likelihood strategy. In this strategy, the absence of a "yes" response results in a "no" response (i.e. if metformin use is not listed anywhere in the chart, it will be

recorded as "no metformin use") [27]. Data was recorded on the data abstraction tool, which was stored on an encrypted USB.

Means and standard deviations were calculated for continuous variables to describe the study population (Table 1). Mann-Whitney U test was used to determine significance for these variables, all of which were not normally distributed (as determined by the Shapiro-Wilk test of normality). Cross-tabulation and the Chi-Square or Fisher's Exact test were used to determine associations for dichotomous variables. Any relationship with a p value <0.05 was deemed statistically significant. Frequency was used to determine the prevalence of B₁₂ deficiency among metformin users. Serum methylmalonic acid (MMA) is a more sensitive and specific marker than serum B₁₂ [7,17-20] since it indicates a metabolic change specific to B₁₂ deficiency [7]; however, MMA labs were not routinely performed in these hospitals. Other studies have demonstrated that some individuals within the marginal or subclinical deficiency range for serum B₁₂ value are B₁₂ deficient with the use of MMA [28,29]. Statistical analyses were performed using SAS v 9.4.

Results

The sample consisted of 106 individuals on metformin and 552 individuals not on metformin. The participant characteristics are shown in (Table 1). Among metformin users, 51% were female, with an average age of 73 years, approximately 54% showed at least 1 symptom of B₁₂ deficiency, and 37% were supplemented with varying doses of B₁₂. Mean serum B₁₂ was not significantly different between metformin users and non-metformin users (413 ± 273 pmol/L vs. 383 ± 204, p=.2725). There were no significant differences in sex, age, signs of B₁₂ deficiency or in concentrations for RBC folate, MCV, hemoglobin, serum iron, creatinine or albumin. There were no differences between metformin users and non-metformin users for medication and supplement use. However, when looking at differences for medication and supplement use within metformin users, there are significant differences (Table 1). Of those taking Metformin, a significantly higher proportion were also taking PPIs compared to those who were not (66% vs 34%, P=0.0010) but the reverse was true for H2 blockers. The majority of metformin users did not use any form of vitamin or mineral supplement.

There was information on B₁₂ status for 391 patients. The overall rate of impaired B₁₂ status (< 220 pmol/L) among the entire patient population with B₁₂ data was 18.6% (n=391) and 24% among metformin users (n=78, P < 0.0001). For non-metformin users, the overall rate was 17%. The overall prevalence of B₁₂ deficiency and subclinical deficiency among metformin users versus non-metformin users was 0.5% vs 4% and 4% vs 10% respectively (P=0.1094) (Table 2). Looking at only metformin users, we can see that the majority of users are classified as having good B₁₂ status (> 220 pmol/L, P=0.0001).

A total of 220 patients were taking some form of B₁₂ supplement (n= 658, P=<0.0001). Of these 18.6% were either B₁₂ deficient or subclinically deficient and only 66% of those who were either deficient or subclinically deficient were taking a B₁₂ supplement. The information on B₁₂ supplement use among patients taking metformin is shown in (Table 3). Only 42% of metformin patients were taking a B₁₂ supplement. Overall, 11 (14%) patients with either B₁₂ deficiency or subclinical deficiency status were taking a B₁₂ supplement versus 8 (10%) patients also with compromised status who were not taking a supplement (P=0.1138).

Table 1: Characteristics of metformin users and non-metformin users identified through a chart review.

Participant characteristic	n	On metformin (n=106)	No metformin (n=552)	p-value
Demographic				
Female, n (%)	336	54 (8)	282 (43)	0.978
Male, n (%)	322	52 (8)	270 (41)	
Age, mean ± SD		73.4 ±13.3	72.9 ±16.5	0.638
Clinical				
Signs of B ₁₂ deficiency, n (%)	384	57 (15)	327 (85)	0.296
Biochemical, mean ± SD				
Serum B ₁₂ (pmol/L)	391	413.7 ±273.8	383.2 ±204.1	0.358
RBC folate (nmol/L)	109	1469.6 ±471.5	1388.4 ±468	0.300
MCV (fL)	631	91.4 ±5.3	91.8 ±5.4	0.409
Hemoglobin (g/L)	631	122.9 ±18.3	125.3 ±19.5	0.164
Serum iron (umol/L)	103	8.4 ±4.0	9.7 ±7.5	0.903
Creatinine (umol/L)	621	80.6 ±30.7	91.6 ± 78.7	0.921
Albumin (g/L)	631	37.6 ±4.5	36.4 ±5.9	0.150
Taking Metformin only				
Medications/Supplements				
PPI use Y, n (%)		70 (66)		0.0010
N, n (%)		36 (34)		
H ₂ blocker use Y, n (%)		11(10)		<0.0001
N, n (%)		95 (90)		
B ₁₂ supplement use Y, n (%)		39 (37)		0.0065
N, n (%)		67 (63)		
Iron supplement use Y, n (%)		21 (20)		<0.0001
N, n (%)		85 (80)		
Folic acid supplement use Y, n (%)		1 (0.9)		<0.0001
N, n (%)		105 (99)		
Multi-vitamin/mineral use Y, n (%)		30 (39)		<0.0001
N, n (%)		76 (71)		

Abbreviation: SD: Standard Deviation; RBC: Red Blood Cell; MCV: Mean Corpuscular Volume; PPI: Proton Pump Inhibitor.

Table 2: Prevalence of B₁₂ deficiency among patient population with B₁₂ data by metformin use (n=391).

B ₁₂ cut-off (pmol/L) ^a	On metformin n (%)	Not on metformin n (%)	p-value
< 148	2 (0.5)	14 (4)	0.1094
148-220	17 (4)	40 (10)	
>220	59 (15)	259 (66)	

^aB₁₂ cut-offs defined as < 148 = deficient, 148-220= marginal status, >220 = normal range.

Table 3: Prevalence of vitamin B₁₂ supplementation and impaired B₁₂ status among metformin users (n=78).

B ₁₂ cut-off (pmol/L) ^a	On B ₁₂ supplement, n (%)	Not on B ₁₂ supplement, n (%)	p-value
<148	2(3)	0 (0)	0.1272
148-220	9 (12)	8 (10)	
>220	22 (28)	37 (47)	

Differences in supplement use by hospital location were also assessed for metformin users (Table 4). Both patients who were

classified as being B₁₂ deficient (<148 pmol/L) were both located at 1 hospital and both were taking B₁₂ supplements. There is a trending towards significance for B₁₂ supplement use by hospital location among those with subclinical B₁₂ deficiency status with one hospital more likely to recommend use of supplements than the other two locations (P=0.0618).

Discussion

It has been well documented that 10-30% of metformin users experience B₁₂ malabsorption [2,3,5-14]; however, there is minimal research on the prevalence of B₁₂ deficiency or subclinical deficiency among metformin users. This study found a 24 % prevalence of either B₁₂ deficiency (≤148 pmol/L) or subclinical deficiency status (<220 pmol/L) among metformin users compared to 17 % for non-metformin users. This value is similar to a previous study, which reports a prevalence rate of 23% in metformin users [15]. or to a study by Pflipsen, et al. [20] which reports a prevalence of 22% among individuals with type 2 diabetes. Despite the higher prevalence rates of deficiency within the metformin population compared to the general patient population in this study, the results were not statistically significant perhaps due to the overall low rate of metformin users and lack of B₁₂ data.

Table 4: Prevalence of B₁₂ supplementation among metformin users by hospital location.

B ₁₂ cutoff (pmol/L)	B ₁₂ supplement use at various hospital sites n (%)						n	p-value
	Site 1		Site 2		Site 3			
	Y	N	Y	N	Y	N		
< 148	-	-	2	-	-	-	2	
148-220	0	3(18)	1 (6)	2 (12)	8(47)	3 (18)	17	0.0618
>220	3 (5)	7 (12)	1 (2)	4 (7)	18 (30)	26 (44)	59	0.5732

Y: Yes, N: No.

Approximately one-third of the entire patient population were taking a B₁₂ supplement. In metformin users, the two patients who were B₁₂ deficient (< 148 pmol/L) were taking a B₁₂ supplement (although there is no record of the actual recommended dosage) but it was even chance as to whether or not those with subclinical B₁₂ deficiency would be taking a B₁₂ supplement. Evidence suggests that larger doses [3] and longer durations [3,4,14] of metformin use are risk factors for B₁₂ deficiency. The retrospective nature of this study prevented dose and duration of metformin from being adequately assessed. There also seemed to be a slight difference in the recommendations for B₁₂ supplementation in metformin users in those with subclinical B₁₂ deficiency by clinic site with the results of this study trending towards significance. This may be related to the lack of a standard cut-off value and different institutions may use a different cut-off. Or this variation in treatment may be due to lack of awareness that neurological impairment and other symptoms of lack of B₁₂ may occur in those with subclinical B₁₂ deficiency if MMA tests are not used to test for functional status.

If individuals with a B₁₂ deficiency do not receive adequate treatment in a timely manner, neurological damage may become irreversible. Treatment options include discontinuing metformin and managing type 2 diabetes through an alternative oral drug or administering B₁₂ supplementation, either orally or intramuscularly [13]. Tissue B₁₂ deficiency can occur without serum B₁₂ deficiency [20]; therefore clinicians should consider screening for B₁₂ using a higher cut-off value to identify all patients at risk or requesting functional markers of B₁₂ status like MMA. In summary, it is recommended that all patients who are taking metformin, be screened for possible vitamin B₁₂ deficiency including blood work for serum methylmalonic acid and serum B₁₂. If the patient is deemed to be B₁₂ deficient, using serum B₁₂ of <220 pmol/L, B₁₂ supplementation should be started immediately. All patients should also be monitored weekly until levels reach normal values. This protocol should be implemented in all health care facilities.

Limitations

The retrospective nature of this study design poses a limitation. Data were collected from electronic records, which lacked information on drug and supplement use, dose, and duration before admission. Therefore, metformin dose and duration could not be reliably analyzed as risk factors for B₁₂ deficiency. However, the primary objective of determining the prevalence of B₁₂ deficiency in various clinical settings was sufficient with this study design.

Another limitation of this study was the sole use of serum B₁₂ concentration, without the use of serum methylmalonic acid to confirm deficiency. There is no consensus as to whether serum B₁₂ concentration accurately reflects storage levels [3,6].

Conclusion

B₁₂ deficiency among metformin users has been well documented. The high prevalence of deficiency in various clinical settings in this study suggests that a protocol for B₁₂ screening is absolutely necessary. All individuals on metformin therapy should receive annual screening for B₁₂ deficiency. Individuals who are at risk should receive supplementation to reduce the possibility of developing serious complications associated with B₁₂ deficiency. Further research is necessary to determine if metformin dose and duration are significantly associated with B₁₂ deficiency in various clinical settings.

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