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Assessment of vitamin B_{12} deficiency and B_{12} screening trends for patients on metformin: a retrospective cohort case review

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ABSTRACT

Objectives Our study investigated the use of vitamin B_{12} testing in a large cohort of patients on metformin and assesses appropriateness and benefits of screening recommendations for vitamin B_{12} deficiency.

Design This retrospective cohort study included insured adult patients who had more than 1 year of metformin use between 1 January 2010 and 1 October 2016 and who filled at least two consecutive prescriptions of metformin to establish compliance. The comparison group was not exposed to metformin. Primary outcome was incidence of B_{12} deficiency diagnosed in patients on metformin. Secondary outcome was occurrence of B_{12} testing in the patient population on metformin. Records dated through 31 December 2018 were analysed.

Setting Large hospital system consisting of inpatient and outpatient data base.

Participants A diverse, adult, insured population of patients who had more than 1 year of metformin use between 1 January 2010 and 1 October 2016 and who filled at least two consecutive prescriptions of metformin.

Results Of 13 489 patients on metformin, 6051 (44.9%) were tested for vitamin B_{12} deficiency, of which 202 (3.3%) tested positive (vs 2.2% of comparisons). Average time to test was 990 days. Average time to test positive for deficiency was 1926 days. Factors associated with testing were linked to sex (female, 47.8%), older age (62.79% in patients over 80 years old), race (48.98% white) and causes of malabsorption (7.11%). Multivariable logistic regression showed older age as the only factor associated with vitamin B_{12} deficiency, whereas African-American ethnicity approached significance as a protective factor.

Conclusions Based on our study's findings of vitamin B_{12} deficiency in patients on metformin who are greater than 65 years old and have been using it for over 5 years, we recommend that physicians consider screening in these populations.

INTRODUCTION

Vitamin B_{12} is a water-soluble vitamin. The human body extracts vitamin B_{12} via gastric acid and intrinsic factor, which is subsequently absorbed in the terminal ileum.[1 2] Patients who suffer from decreased ileal absorption are considered at increased risk of vitamin B_{12} deficiency.[1 2] Other risk factors include decreased intrinsic factor production and decreased dietary intake.[1 2] Medications including proton pump inhibitors, histamine H2 blockers and metformin have also been shown to cause vitamin B_{12} deficiency.[1 2]

Although the exact mechanism is unknown, metformin's ability to cause vitamin B_{12} deficiency is well established in the literature.[3] The first reports describing this association were published in the late 1960s.[4] A large meta-analysis of 19 intermediate and high-quality rated studies confirmed that patients on metformin will likely have lower vitamin B_{12} levels.[5] Another study showed that when the dose of metformin was increased by 100 mg, the odds for vitamin B_{12} deficiency increased by 8%.[6] Other studies reported similar findings.[7] However, findings on the duration of metformin use and its effect on B_{12} deficiency are inconsistent.[6–9]

The reported prevalence of vitamin B_{12} deficiency from metformin ranges from 5.8% to 52%.[5–7 10 11] Although no formal screening guidelines exist, the American Diabetes Association recommends that patients with long-term use of metformin, specifically those with anaemia or peripheral neuropathy, have vitamin B_{12} levels measured periodically.[12] These recommendations are based on one of the largest and longest studies (over 2000 patients across 27 centres in the USA) reporting that patients on metformin, especially long-term use, are at higher risk for vitamin B_{12} deficiency.[13] The Agency for Healthcare Research and Quality recommends screening for vitamin B_{12} deficiency in patients on long-term proton pump inhibitors or H2 blockers (>12 months) and metformin (>4 months).[14]

In our study, we aimed to investigate use of vitamin B_{12} testing in a large cohort of patients

on metformin and assess the benefit to formulating screening recommendations for vitamin B_{12} deficiency.

METHODS

Study population

We received access to an administrative database of a non-profit health insurance plan offered by our hospital system to identify our system's insured adult patients (≥18 years) who had more than 1 year of metformin use between 1 January 2010 and 1 October 2016 and who filled at least two consecutive prescriptions of metformin. Using the criteria of filling at least two consecutive prescriptions of metformin and more than 1 year of metformin use, we assumed patient compliance to regularly taking the medication. Exclusion criteria included history of vitamin B_{12} deficiency, a single prescription of metformin filled, and first metformin prescription filled within 30 days of insurance, as duration of metformin use could not be determined. Patients with only one prescription filled were deemed to be noncompliant with the medication and were excluded.

The comparison population included insured adult patients in the database within the same time frame who were not exposed to metformin.

Records dated through 31 December 2018 were analysed for vitamin B_{12} testing and deficiency.

Measurements of metformin and outcome variables

Metformin use was determined from filled prescriptions by patients in the health plan database for the study period. We included all available doses, brands and combination pills of metformin. The main outcome variables were presence of testing for vitamin B_{12} and vitamin B_{12} deficiency defined as <180 pg/mL (determined by our institution laboratory department). Our institution uses Beckman Coulter DxI immunochemistry systems for vitamin B12 testing.[15]

Data on additional covariates were collected from the health system's administrative databases, including demographic information (age, sex and race/ethnicity) and proton pump inhibitor use. Age was categorised into quintiles (18–39 years old, 40–49 years old, 50–64 years old, 65–79 years old and >80 years old based on population distribution). Confounder variables included malabsorption syndromes including small bowel disease, malnutrition, coeliac disease and previous bariatric surgery based on diagnosis and procedure codes in administrative data.

Screening guidelines

To be recommended for routine screening, a test such as vitamin B_{12} must meet certain criteria based on Wilson and Jungner's principles of screening: (1) the disease is appropriate for screening (ie, the disease is serious, early treatment is beneficial and there is a high prevalence of preclinical disease); (2) screening is feasible and effective (eg, acceptable, cost-effective and detects many cases) and (3) the screening test is valid and widely available.[16 17] We kept these criteria in mind while performing our study and reviewed a random sample of charts to compare findings with these routine screening criteria.

Statistical analyses

Sample characteristics were described using mean and SD for continuous variables and frequencies (numbers and percentages) for categorical variables. Bivariate analysis was used to examine the effect of each of the covariates on incidence of testing and B_{12} deficiency. Multivariable logistic regression models were used to examine the associations between metformin use and vitamin B_{12} deficiency, adjusting for all other covariates. All analyses were performed using Epi Info V.7 (Centers for Disease Control and Prevention, Atlanta, Georgia).

RESULTS

Of 13 489 patients exposed to metformin, the majority were women (3461, 53.7%), aged 50–64 years (2316, 43.2%) to 65–79 years (2285, 31.1%) and African-American (2251, 40.1%) or white (2869, 43.4%) (table 1). Of the metformin exposed group, 6051 (44.9%) were tested for B_{12} deficiency, of whom 202 (3.3%) were found to be B_{12} deficient. The mean time between metformin initiation and B_{12} testing was 972 days (the median time was 720 days). The mean time between metformin initiation and incidence of B_{12} deficiency was 1926 days (5.3 years) (the median time was 2313 days).

Stratifying by demographics, men were tested for B_{12} deficiency less often than women (41.5% vs 47.8%; OR 0.7568; 95% CI, 0.7047 to 0.8126; p<0.05) (table 2). Thus, men were tested approximately 25% less frequently compared with women. Men were also tested at a later date (mean=1037 days, median=785 days, positively skewed data set) compared with women (mean=922 days, median=675 days, positively skewed data set), which was also statistically significant (Kruskal-Wallis test, p<0.05). However, the vitamin B_{12} deficiency rate in men (3.1%) compared with women (4.0%) was not statistically significant (table 3) (p=0.2031).

Analysis by age group showed that vitamin B_{12} levels were evaluated at a much higher rate among the elderly (table 1). Patients aged 65–79 years and >80 years were tested for B_{12} deficiency at a rate of 54.5% and 62.8%, respectively, higher than patients younger than 65 years old (<40% for ages 18–64 years). With each increase in age quintile, there was a 45% more likelihood of having B_{12} levels evaluated (p<0.05). An older subgroup of patients (age >65 years) showed a B_{12} deficiency rate of at least 4.2% compared with 2.5% in younger patients (p<0.05). With each increase in age quintile, there was approximately 34% more likelihood of incidence of B_{12} deficiency (p<0.05). The elderly (age >80 years) were tested much sooner after starting metformin than the study population (mean of 785 days vs 970 days) and were found to have B_{12} deficiency much sooner than the study population (mean of 1491 days vs 1926 days).

Table 1 Characteristics of the population and associated testing

	Total no	Ever tested	Mean days to test	Median days to test	Deficiency	Mean days to B_{12} deficiency	Median days to B_{12} deficiency
Gender							
Male	6247 (46.3%)	2590 (41.5%)	1037	785	81 (3.1%)	1883	1921
Female	7242 (53.7%)	3461 (47.8%)	922	675	121 (3.5%)	1955	2407
Total	13489 (100%)	6051 (44.9%)	972	720	202 (3.3%)	1926	2313
Age							
18–39	830 (6.2%)	292 (35.2%)	929	643	3 (1.0%)	2686	2780
40–49	1716 (12.7%)	581 (33.9%)	942	695	12 (2.1%)	2367	2690
50–64	5828 (43.2%)	2316 (39.7%)	1050	780	64 (2.8%)	2019	2397
65–79	4196 (31.1%)	2285 (54.5%)	952	723	99 (4.3%)	1894	2076
>80	919 (6.8%)	577 (62.8%)	785	553	24 (4.2%)	1492	1133
Total	13489 (100%)	6051 (44.9%)	972	720	202 (3.3%)	1926	2313
Race							
African-American	5409 (40.1%)	2251 (41.6%)	966	724	59 (2.6%)	2132	2407
Asian	499 (3.7%)	209 (41.9%)	905	684	6 (2.9%)	2312	2680
Hispanic	338 (2.5%)	149 (44.1%)	1184	791	6 (4.0%)	2230	2500
Other/unknown	1385 (10.3%)	573 (41.4%)	969	692	22 (3.8%)	1756	2165
Caucasian	5858 (43.4%)	2869 (49.0%)	970	723	109 (3.8%)	1811	2040
Total	13489 (11%)	6051 (44.9%)	972	720	202 (3.3%)	1926	2313
Confounders							
Malabsorption disorders	694 (5.1%)	498 (71.8%)	860	572	11 (2.2%)	1864	2046
Proton pump inhibitor use (prescriptions)	3957 (29.3%)	2173 (54.9%)	947	703	70 (3.2%)	2058	2452
Total	4651 (100%)	2671 (57.4%)	972	720	81 (3.0)	1926	2313

Analysis by race showed no significant difference in rates of testing, rates of B_{12} deficiency, days between metformin initiation and B_{12} testing or days between metformin initiation and detection of B_{12} deficiency. However, the African-American population was tested at a lower rate (41.62%) compared with the non-African-American population (44.9%), showing a 15% less likelihood of being tested compared with the other ethnic groups (p<0.05). The incidence of B_{12} deficiency in the African-American group was 27% lower than other races, which approached statistical significance (p=0.051) (table 3).

Evaluation of patients with malabsorption disorders who were started on metformin showed a much higher B_{12} testing rate than the entire study population (70% vs 44.86%). Patients with malabsorption disorders were 3.64 times more likely to be tested than patients without malabsorption disorders (p<0.01). The incidence of vitamin B_{12} deficiency in this group, however, was not significantly lower than the total study population (2.2% vs 3.34%, p=0.38). Patients using proton pump inhibitors while on metformin were 64% more likely to be tested for vitamin B12 deficiency (p<0.05); however, the B_{12} deficiency rate was not statistically significant.

Table 2 Logistic regression analysis: ever tested for B_{12} deficiency

	OR	95% CI	P value
Age	1.46	1.402 to 1.514	**<0.001**
AfricanAmerican	0.85	0.793 to 0.918	**<0.001**
Malabsorption syndromes	3.64	3.064 to 4.334	**<0.001**
Male	0.76	0.705 to 0.813	**<0.001**
Proton pump inhibitor use	1.64	1.519 to 1.771	**<0.001**

Bold values are statistically significant.

Table 3 Logistical regression analysis: B_{12} deficiency

	OR	95% CI	P value
African-American	0.73	0.534 to 1.001	0.05
Age	1.34	1.141 to 1.573	**<0.001**
Male	0.83	0.619 to 1.107	NS
Malabsorption syndromes	0.76	0.407 to 1.409	NS
Proton pump inhibitor use	0.92	0.681 to 1.233	NS

Bold values are statistically significant.
NS, not statistically significant.

Of the 202 charts indicating B_{12} deficiency, we reviewed a random sample of 105 charts to identify the most common reasons for vitamin B_{12} testing in our study population. Anaemia (26%), cognitive decline (17%) and neuropathy (16%) were the most commonly reported reasons, whereas only 3.8% stated that the B_{12} level was ordered for concern of deficiency caused by metformin.

DISCUSSION

In our study population, individuals on metformin were tested for vitamin B_{12} deficiency more frequently if they were elderly, had a malabsorption disorder, or were taking proton pump inhibitors. African-American patients were tested less frequently compared with other races, and men were tested less frequently compared with women. The only factor associated with vitamin B_{12} deficiency, however, was older age. African-American ethnicity approached significance as a protective factor for B_{12} deficiency.

While we found testing to be suboptimal, the incidence of vitamin B_{12} deficiency for patients on metformin was lower than we had expected (3.3% vs 2.2% comparison). Our findings are concordant with the Diabetes Prevention Programme Outcomes Study (DPPOS) (B_{12} deficiency rate of 4.3% vs placebo deficiency rate of 2.4%).[13 18] The DPPOS study population consisted of 68% women, 45% from ethnic and racial minority groups, and 20% aged 60 years or older.[13 18] Our study consisted of 53% women and 56.6% minorities. The DPPOS did not distinguish between the different minority races in their report.[13 18] The DPPOS study defined B_{12} deficiency as <203 pg/mL, a higher value compared with our definition.[13 18] Another large study that used data from the National Health and Nutrition Examination Survey (NHANES) also showed similar B_{12} deficiency results.[19] Their study had 49.4% women, but few minorities (14.6% African-American and 10.9% Hispanic).[19] Their definition of B_{12} deficiency was <148 pmol/L, a lower value compared with our definition.[19] The rate of B_{12} deficiency of the NHANES study population without diabetes was similar to ours.[19]

Our study's racial composition was different from other large studies. With our population including 40% African-Americans, our results showed that this ethnicity was less likely to be deficient in B_{12}. The US population includes 13.4% African-Americans.[20] The NHANES and DPPOS studies did not have large African-American populations but found similar results regarding their lower B_{12} deficiency rates. This finding suggests a possibility that the African American race may be protective from vitamin B_{12} deficiency, but more research is needed to explore this hypothesis, as the African-American group was tested at lower rates. This could be a factor that influenced the diagnosis of B_{12} deficiency, as, historically, African-Americans have remained undiagnosed in other cases.

Our study showed that patients using metformin for more than 5 years were at greater risk for vitamin B_{12} deficiency. The study using NHANES data found that the likelihood of vitamin B_{12} deficiency was greater the longer patients took metformin (B_{12} deficiency rate of 4.1% when on metformin for 3–10 years vs 8.1% for >10 years).[19] The DPPOS study found that patients on metformin had a similar B_{12} deficiency prevalence at 5-year follow-up compared with patients in the NHANES study.[13] Given that our results are similar to both studies, we agree that longer use of metformin may increase the likelihood of B_{12} deficiency.

We also found increased age to be correlated with vitamin B_{12} deficiency in our study. The NHANES study found the rate of B12 deficiency to increase by a factor of 1 with each year of age[19] whereas the DPPOS study found no relation between age and B_{12} deficiency.[13] This is a particularly important point as studies have shown that metformin can be useful in the treatment of cancers, obesity, liver diseases, renal diseases and cardiovascular diseases which tend to plague older populations.[21]

We used results from our study to analyse whether the 1.2% difference in vitamin B_{12} deficiency rates between our metformin and comparison populations was significant enough to indicate the need for screening for B_{12} deficiency. Using criteria for creating a screening guideline, not all can be met. Vitamin B_{12} deficiency can cause many symptoms that can be reversed with vitamin B_{12} supplementation. Supplementation is not expensive; an injection at our health system is approximately US$10 and is usually covered by insurance. The test for B_{12} deficiency, however, is not affordable at this time. Patients at our institution are charged US$80 per B_{12} test, which would only be covered if associated with a symptom of deficiency as predetermined by the patient's insurance. As indicated by a random sample chart review, 59% of our patients had symptoms of B_{12} deficiency (eg, anaemia, neuropathy or cognitive decline) that led to testing vs true screening. This correlates with the current recommendations.

Our study is unique in that we were able to distinguish the rates at which testing occurred and the rates at which different populations were tested. Neither the DPPOS nor NHANES study reported these rates. We found that women were tested more than men, older patients were tested more frequently compared with their younger counterparts, and African-Americans were less likely to be tested. Many factors account for the testing habits of physicians based on these populations' characteristics. More research regarding this topic is necessary.

Our study has several limitations. Due to the retrospective design, we were not able to completely address all potential confounders such as dietary habits, nutritional status, metformin use and vitamin B_{12} supplementation. We used data that were coded in our electronic medical system. Our study did not stratify based on metformin dosing or duration of metformin prescription (30 days vs 90 days). Our patients were insured under a premium insurance plan that includes few Medicare patients and no Medicaid patients. This limits the generalisability of the study and could potentially lead to selection bias, but helped us confirm that the patient filled some scripts of

metformin. Metformin compliance could not be verified, although we excluded patients with less than two filled metformin prescriptions and those who filled a metformin prescription within 30 days of starting their insurance. Nutritional status was not accounted for, including over-the-counter supplements and vegan and vegetarian diets. We defined vitamin B_{12} deficiency as <180 pg/mL whereas other studies used <203 pg/mL, which makes study comparisons more difficult.

Despite its limitations, our study accounted for confounders and excluded preexisting vitamin B_{12} deficiency to assess incidence and not prevalence. We used a single insurance database to confirm that metformin prescriptions were filled by our patients and to estimate duration of metformin use via documentation of the first and subsequent filled prescriptions. Our study population was diverse and overall included more minorities than white patients.

CONCLUSION

Our study findings suggest that physicians should be cognizant of the increased incidence of vitamin B_{12} deficiency in select populations. These populations include patients with greater than 5 years of metformin use and age greater than 65 years old. The patient's race should also be considered.

What this paper adds

- Question: Should we screen for vitamin B_{12} deficiency in patients taking metformin?
- Findings: Patients who are greater than 65 years old and patients who have been taking metformin for more than 5 years are at increased risk. The black population is also likely at increased risk.
- Meaning: Consider screening for B_{12} deficiency in these populations even if they are asymptomatic for the deficiency.

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Contributors DM, JT, LL and KB set up the data protocol, performed chart review, analysed and interpreted the data and took the lead in the writing process. MS made substantial contributions to the conception and design, and actively participated in writing manuscript and interpreting data. DM is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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